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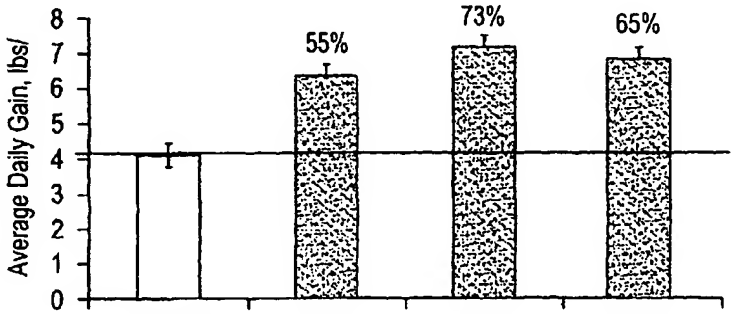

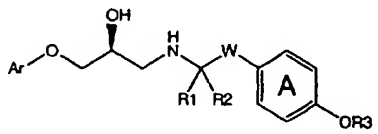

(I)

(57) Abstract: Disclosed is a method of treating a subject with a Wasting Syndrome. The method comprising the step of administering to the subject an effective amount of a compound represented by Structural Formula (I), Ar is a substituted or unsubstituted aryl group. Ar is preferably a monocyclic heteroaryl group or a fused polycyclic heteroaryl group. Ring A has zero, one or more additional substituents. R1 and R2 are independently -H or a C1-C4 alkyl group. W is $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$. R3 is a substituted or unsubstituted phenyl or pyridyl group.

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TREATING WASTING SYNDROMES WITH ARYLOXY PROPANOLAMINES

BACKGROUND OF THE INVENTION

The development of biologically active agents which promote the growth of muscle mass would greatly improve a physician's ability to treat patients suffering from Wasting Syndromes. As used herein, a "Wasting Syndrome" is a disease or condition which causes, is characterized by, or is accompanied by a loss of muscle mass and/or strength. Diseases which cause or are accompanied by loss of muscle mass include AIDS, cancer, muscle denervation diseases (e.g., multiple sclerosis and amyotropic lateral sclerosis), dystrophic disease (e.g., muscular dystrophy) and eating disorders (e.g., anorexia and bulimia). Loss of muscle mass can also occur, for example, in individuals undergoing certain types of cancer chemotherapy, as a result of aging, or from muscle deconditioning or atrophy resulting from prolonged immobilization. Causes of prolonged immobilization include being bedridden for an extended period of time, immobilizing a limb in a cast, temporary paralysis resulting from spinal cord injuries, or exposing an individual to a weightless environment such as in outer space.

Anabolic steroids and growth hormones are biologically active agents which are known to build muscle mass.

Unfortunately, their use is accompanied by undesirable side effects. For example, the growth hormones Protropin and Somatropin cause hypercalciuria, hyperglycemia and frank diabetes. Anabolic steroids cause behavioral disorders such as aggression and paranoia, deepening of the voice, increased growth of body hair, sterility, acne and weight

gain. Therefore, these drugs are generally not suitable for treating individuals with Wasting Syndromes.

Certain publications have appeared generally disclosing arylpropanolamines such as U.S. Patent 5,013,761 and WO 97/10825.

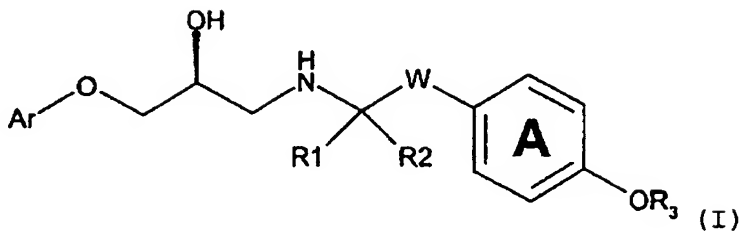
The development of new drugs which can promote the growth of muscle without causing undesirable side effects is, however, urgently needed and would greatly benefit individuals suffering from Wasting Syndromes.

SUMMARY OF THE INVENTION

It has now been found that certain aryloxy propanolamines are anabolic and can promote the growth of muscle mass in mammals. For example, a number of aryloxy propanolamines shown in Tables 1 and 2, including Compounds **1** and **3-18**, decreased the urea nitrogen in the blood serum when injected into or administered orally to cattle (see Examples 17 and 18). A decrease in serum urea nitrogen ("SUN") level is indicative of an anabolic effect. In addition, Compound **4** caused an increase of between about 54% and 73% in average daily weight gain, or an increase of between 4.7% and 6.4% in total body mass due mainly to increased muscle mass when administered orally to cattle over a twenty-eight (28) day period (Example 19). The structures of Compounds **1** and **3-18** are shown in Tables 1 and 2. Based on these discoveries, methods of promoting the growth of muscle mass and methods of treating a subject with a Wasting Syndrome are disclosed.

One embodiment of the present invention is a method of treating a subject with a Wasting Syndrome. The method comprises the step of administering to the subject an

effective amount of a compound represented by Structural Formula (I):



(I)

and physiologically acceptable salts thereof,

wherein:

Ar is a substituted or unsubstituted aryl group and Ar is preferably a monocyclic heteroaryl group or a fused polycyclic heteroaryl group; Ring **A** has zero, one or two additional substituents other than those shown in Structural Formula (I);

R1 and R2 are independently -H or a C1-C4 alkyl group;

W is $-CH_2-$, $-CH_2CH_2$ -or $-CH_2CH_2CH_2-$; and

R3 is a substituted with one, two or three substituents or unsubstituted phenyl or pyridyl group.

Another embodiment of the present invention is a method of promoting muscle growth in a human subject. The method comprises the step of administering to the subject an effective amount of a compound represented by Structural Formula (I).

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a graph showing the average daily weight gain after twenty-eight days of cattle treated with: a) 0.0 mg of Compound **4** per kilogram of body weight per day; 0.125

mg of Compound **4** per kilogram of body weight per day; 0.250 mg of Compound **4** per kilogram of body weight per day; and 0.5 mg of Compound **4** per kilogram of body weight per day.

Figure 2 is a graph showing the feed efficiency ratio after twenty-eight days for cattle treated with: a) 0.0 mg of Compound **4** per kilogram of body weight per day; 0.125 mg of Compound **4** per kilogram of body weight per day; 0.250 mg of Compound **4** per kilogram of body weight per day; and 0.5 mg of Compound **4** per kilogram of body weight per day.

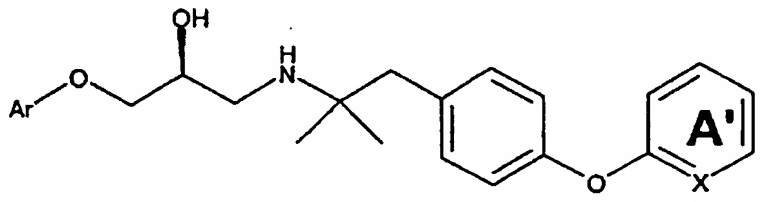
Figure 3 is a graph showing the carcass soft tissue composition of cattle treated with the following over a twenty-eight day period: a) 0.0 mg of Compound **4** per kilogram of body weight per day; 0.125 mg of Compound **4** per kilogram of body weight per day; 0.250 mg of Compound **4** per kilogram of body weight per day; and 0.5 mg of Compound **4** per kilogram of body weight per day.

DETAILED DESCRIPTION OF THE INVENTION

The compounds used in the method of the present invention have anabolic effects and can therefore be used to promote the growth of muscle mass and to therapeutically and/or prophylactically treat subjects with a Wasting Syndrome. The anabolic effects of these compounds are not blocked by cyanopindolol and propanolol, which are known antagonists of the beta 1, beta 2 and beta 3 adrenergic receptors. Specifically, the decrease in blood urea nitrogen levels (BUN) in mice administered Compounds **1** or **3** was about the same in mice pre-treated with cyanopindolol or propanolol compared with mice that had not been pre-treated (Example 12). Although Applicants do not wish to be bound by any particular mechanism, this result is consistent with

the anabolic effects of these compounds resulting from their action at a receptor other than beta 1, beta 2 or beta 3.

In a preferred embodiment, the aryloxy propanolamine used in the methods of the present invention is represented by Structural Formula (II):



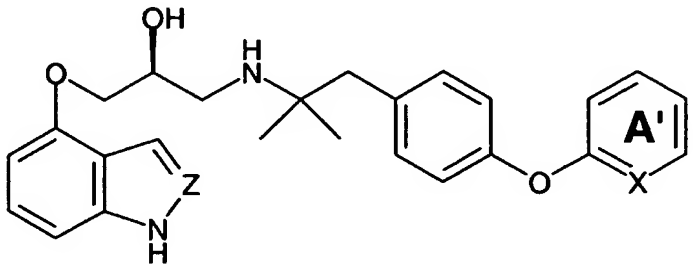
(II)

Ar is as described for Structural Formula (I);

Ring **A'** is unsubstituted or substituted with one or two substituents; and

X is -N- or -CH-.

In a more preferred embodiment, the aryloxy propanolamine used in the methods of the present invention is represented by Structural Formula (III):

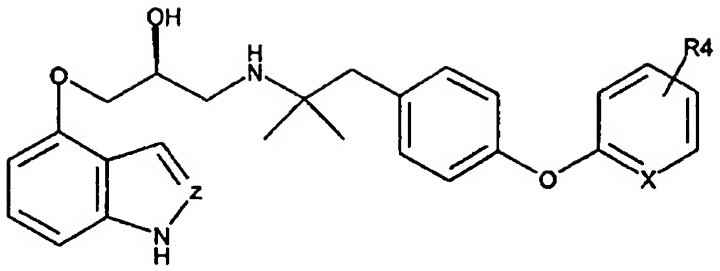


Ring **A'** is as described in Structural Formula (II); and

X is -CH- or N; and

Z is -N- or -CH-.

More preferably, the aryloxy propanolamine used in the methods of the present invention is represented by Structural Formula (IV):



(IV)

X is -CH- or -N-;

Z is -N- or -CH-; and

R4 is -CN, -CONH, or $-SO_2CH_3$.

Even more preferably, the aryloxy propanolamine used in the methods of the present invention is represented by Structural Formula (IV), wherein X is -N-, Z is -CH- and R4 is $-CONH_2$.

Specific examples of compounds which can be used in the methods of the present invention are provided in Tables 1 and 2 and in Examples 17 and 18.

Physiologically acceptable salts of the compounds disclosed herein, including the compounds represented by Structural Formulas (I)-(IV) and the compounds shown in Tables 1 and 2, are also included. Salts can be formed from those compounds which comprise acidic functional groups by reacting with a suitable base. Such salts include those derived from inorganic bases such as ammonium and alkali and alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, as well as salts derived from basic organic amines such as aliphatic and aromatic amines, aliphatic diamines, hydroxy alkamines, and the like. Such bases useful in preparing the salts of this invention thus include ammonium hydroxide, potassium carbonate, sodium bicarbonate, calcium hydroxide, methylamine, diethylamine, ethylenediamine, cyclohexylamine, ethanolamine and the like.

Because of the amine moiety, salts of the compounds disclosed herein can also be prepared by reacting with a suitable acid. Acids commonly employed to form such salts include inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, as well as organic acids such as para-toluenesulfonic, methanesulfonic, oxalic, para-bromophenylsulfonic, carbonic, succinic, citric, benzoic, acetic acid, and related inorganic and organic acids. Such physiologically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, 2-butyne-1,4-dioate, 3-hexyne-2, 5-dioate, benzoate, chlorobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, hippurate, β-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like salts. Glycolate, benzoate, 4hydroxybenzoate and *para*-toluate are preferred salts for Compound **2**; glycolate is especially preferred. Acetate, chloride, oxalate and 4-hydroxybenzoate are preferred salts for Compound **4**; acetate is especially preferred. Hydrochloride is a preferred salt for Compound **6**.

The present invention includes solvates of the compounds of Structural Formula I and the physiologically acceptable salts thereof. A particular compound of the present invention of a physiologically acceptable salt

thereof may form solvates with water or common organic solvents. Such solvates are included within the scope of compounds of the present invention.

In addition, it will be appreciated that diastereomers exist for the compounds of Structural Formula I and, depending on the substituents, further diastereomers may exist. The compounds of the present invention include mixtures of two or more diastereomers as well as each individual stereoisomer.

It will also be appreciated that some of the heterocycles may exist in tautomeric forms. All such forms are included within the scope of the present invention.

Aryl groups include carbocyclic aromatic groups such as phenyl, 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl, and heteroaryl groups such as *N-imidazolyl*, 2-imidazolyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 2-pyranyl, 3-pyranyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl and 5-oxazolyl.

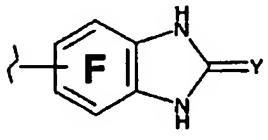
Aryl groups also include fused polycyclic heteroaryl ring systems in which a carbocyclic aromatic ring or heteroaryl ring is fused to one or more other heteroaryl rings. Two rings are "fused" when both rings contain the same two ring adjacent ring atoms. Examples include 1-benzimidazolinyl, 2-benzimidazolonyl, 1-benzimidthioazolinyl, 2-benzimidthioazolonyl, 1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 3-indolyl, 2-quinolinyl, 3-quinolinyl, 2-benzothiazolyl, 2-benzooxazolyl,

2-benzimidazolyl, 2-quinolinyl, 3-quinolinyl, 1-isoquinolinyl, 3-quinolinyl, 1-isoindolyl and 3-isoindolyl.

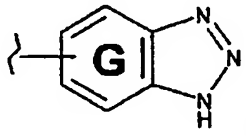
Examples of suitable monocyclic heteroaryl groups and fused polycyclic heteroaryl groups for Ar are shown below in Structural Formulas (V)-(XI):

(V)

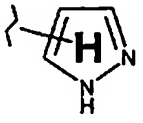
(VI)



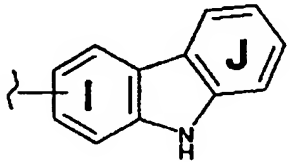
(VII)



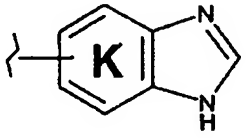
(VIII)



(IX)



(X)

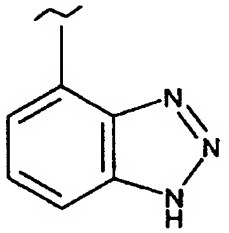


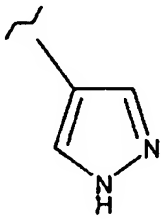
(XI)

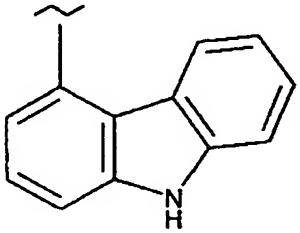
Rings **B-K** are independently substituted with one or two substituents or unsubstituted; and

Y is S or O.

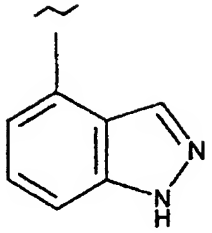
Examples of preferred monocyclic heteroaryl groups and fused polycyclic heteroaryl groups for Ar are shown below in Structural Formulas (XII)-(XVIII):

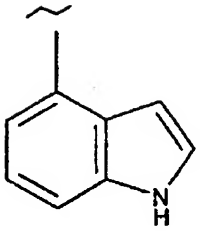


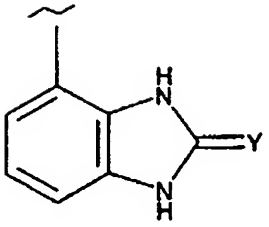




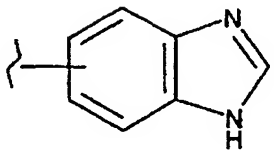
(XII) (XIII) (XIV)







(XV) (XVI) (XVII)



(XVIII)

Y is as described above.

An aliphatic group refers to straight, branched chain or cyclic hydrocarbons having from one to about twenty carbon atoms. The hydrocarbon can be saturated or can have one, two or three units of unsaturation.

Non-aromatic heterocyclic rings are non-aromatic carbocyclic rings which include one, two or three heteroatoms selected from nitrogen, oxygen and sulfur in the ring that will afford a stable structure. The ring can be five, six, seven or eight-membered. Examples include 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl and 4-thiazolidinyl.

Suitable substituents on an aliphatic group, aryl group (carbocyclic and heteroaryl), non-aromatic heterocyclic ring or benzyl group include, for example, -OH, halogen (-Br, -Cl, -I and -F), -OR, -O-COR, -CN, $-NO_2$, -COOH, $-NH_2$, -NHR,

$-NR_2$, -COOR, -COR, -CHO, $-CONH_2$, -CONHR, $-CONR_2$, -SH, -SR and -NH-C (=NH) $-NH_2$. R is a C1-C6 alkyl, benzyl or phenyl. A substituted nonaromatic heterocyclic ring can also have =O, =S, =NH or =NR where R is as defined above, as a substituent. A substituted aliphatic, substituted aromatic, substituted nonaromatic heterocyclic ring or substituted benzyl group can have one, two or three substituents.

In the structural formulas depicted herein, the bond by which a chemical group or moiety is connected to the remainder of the molecule or compound is indicated by the following symbol:

For example, the corresponding symbol in Structural Formulas (V)-(XVIII) indicates the bond by which the depicted aryl group is connected to the 3-oxygen atom of the molecule represented by Structural Formula (I),(II), (III) or (IV).

A "subject" is a mammal in need of treatment, therapeutically or prophylactically, for a Wasting Syndrome or in need of muscle mass growth to prevent an adverse effect on health. The subject is preferably a human. However, a "subject" can also be an animal in need of such treatment, e.g., a companion animal (e.g., horse, dog, cat, and the like) or a laboratory animal (e.g., rat, mouse, guinea pig, and the like).

A Wasting Syndrome is a disease or condition which results in, is characterized by or accompanied by a loss of muscle mass and/or strength. Examples of such diseases include AIDS; cancer; demyelinating disorders resulting in muscle atrophy (e.g., multiple sclerosis, amyotropic lateral sclerosis, congenital metabolic disorders such as phenylketonuria, Tay-Sachs disease, Hurler's syndrome and leukodystrophies, postinfections encephalomyelitis, viral

encephalitis, aseptic meningitis and HTLV-associated myelopathy); dystrophic disease (e.g., muscular dystrophy, Duchenne dystrophy, Landouzy-Dejerine muscular dystrophy, and limb-girdle muscular dystrophy); generalized and focal dystonia; eating disorders (e.g., anorexia and bulimia); cachexia or wasting due to chronic diseases; and vascular disorders (e.g., infarction). Loss of muscle mass and/or strength can also occur in subjects undergoing certain types of chemotherapy, or as a consequence of aging, malnutrition, or muscle deconditioning. Muscle deconditioning commonly occurs in individuals who experience a prolonged period in a weightless environment such as outer space, are bedridden for extended period of time, or have certain muscles or muscle groups immobilized, such as in a cast. Individuals requiring prolonged bedrest include those with chronic diseases and those suffering from temporary paralysis from spinal cord injuries resulting from, for example, hematoma or compression.

An "effective amount" is the quantity of compound which can promote the growth of muscle mass. Alternatively, an "effective amount" is the quantity of compound which can prevent, slow, arrest or reverse the loss of muscle mass and strength resulting from Wasting Syndromes. Typically, an effective amount of the compound can range from about 0.01 mg/kg to about 20 mg/kg of the active compound of this invention. Preferred daily doses will be about 0.2 to about 10 mg/kg, more preferably about 0.3 to about 5 mg/kg. The amount of compound administered to the individual will depend on the type and severity of the disease or condition and on the characteristics of the individual, such as general health, age, sex, body weight and tolerance to drugs. It will also depend on the degree, severity and type

of disease or condition. The skilled artisan will be able to determine appropriate dosages depending on these and other factors.

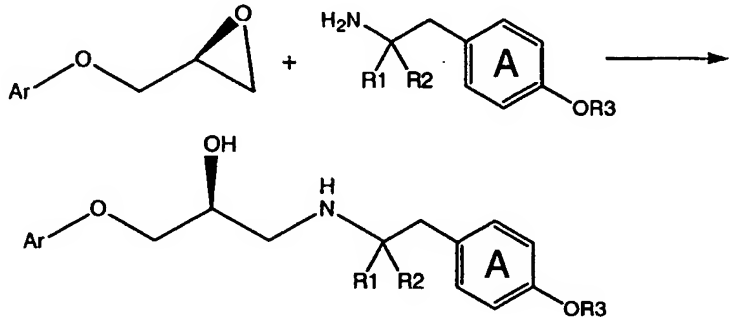
The anabolic agents of the present invention can be administered by any suitable route, including, for example, orally in capsules, suspensions or tablets or by parenteral administration. Parenteral administration can include, for example, systemic administration, such as by intramuscular, intravenous, subcutaneous, or intraperitoneal injection or implant patch or transdermal depot. The compound can also be administered orally (e.g., dietary), topically, by inhalation (e.g., intrabronchial, intranasal, oral inhalation or intranasal drops), or rectally, depending on the disease or condition to be treated. Oral is a preferred mode of administration.

The compounds used in the method of the present invention can be administered to the subject in conjunction with an acceptable pharmaceutical carrier or diluent as part of a pharmaceutical composition for treatment of a Wasting Syndrome or for the promotion of muscle growth. Formulation of the compound to be administered will vary according to the route of administration selected (e.g., solution, emulsion, capsule). Suitable pharmaceutical carriers may contain inert ingredients which do not interact with the compound. Standard pharmaceutical formulation techniques can be employed, such as those described in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. Suitable pharmaceutical carriers for parenteral administration include, for example, sterile water, physiological saline, bacteriostatic saline (saline containing about 0.9% mg/ml benzyl alcohol), phosphate-buffered saline, Hank's solution, Ringer's-lactate

and the like. Methods for encapsulating compositions (such as in a coating of hard gelatin or cyclodextran) are known in the art (Baker, *et al.*, "Controlled Release of Biological Active Agents", John Wiley and Sons, 1986).

The compounds of the present invention can be prepared by procedures disclosed in WO 97/10825 to Bell *et al.*, WO 98/09625 to Crowell *et al.*, U.S. Patent No. 5,808,080 and U.S. Patent No. 6,046,227. The entire teachings of these references are incorporated herein by reference. Reactions for preparing these compounds are shown below in Scheme I:

Scheme I

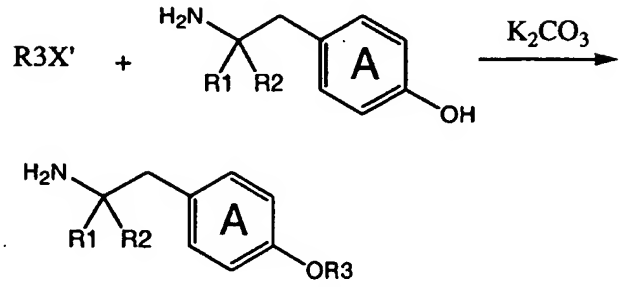


Ar, R1-R3 and Ring **A** are as described above in Structural Formula (I).

The amination of the epoxides in Scheme I is carried out under conditions known in the art for this type of reaction. For example, the epoxide may be combined with the amine in an alcohol, preferably, ethanol at room temperature to the reflux temperature of the reaction mixture. For example, the reaction is carried under conditions generally described in Atkins *et al.*, *Tetrahedron Letters* 27:2451 (1986) the entire teachings of which are incorporated herein by reference. An example of specific conditions for reacting an epoxide with an amine is provided in Examples 5 and 5A.

The amine starting material in Scheme I is prepared as shown below in Scheme II:

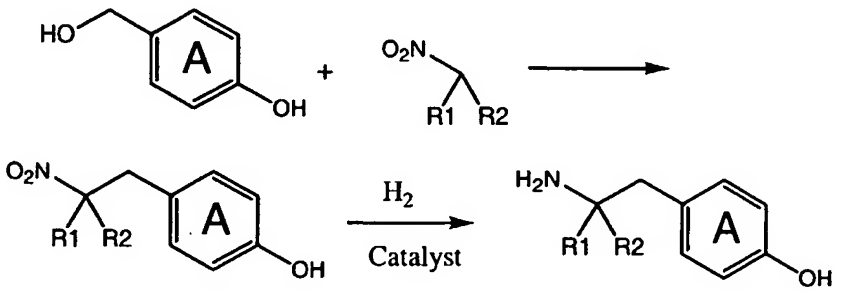
Scheme II



R1-R3and Ring A in Scheme II are as described in Structural Formula (I). X' is a halide. The coupling can be carried out according to procedures well known in the art and is preferably performed by mixing the starting materials in N,N-dimethylacetamide and toluene in the presence of potassium carbonate. The reaction is then heated to reflux for about 5 to about 24 hours, and the water removed. The product is isolated by standard techniques. The crude product can be purified by methods well known in the art. Specific conditions for carrying the reaction shown in Scheme II are provided in Examples 4 and 4A.

The amine starting material in Scheme II is prepared as shown below in Scheme III:

Scheme III

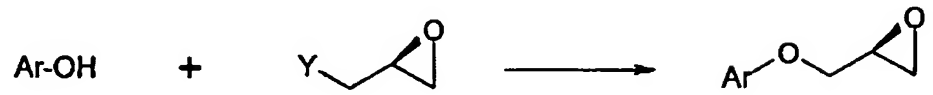


"Nitro Int rmediate"

R1-R2 and Ring **A** in Scheme III are as described in Structural Formula (I). The nitro intermediate can be prepared by reacting 4-hydroxybenzyl alcohol with an excess (about 5 mol/equiv) of the nitro starting material by methods described in *Sh. Prikl. Kin., Vol.* 45, 157377 (1972), the entire teachings of which are incorporated herein by reference. The reaction can also be carried out by mixing the reagents in an aprotic solvent, preferably diglyme, and adding potassium *t*-butoxide (0.5 mol/equiv.). The reaction is then heated to reflux and water removed. When removal of water is complete, generally after about 28 hours depending upon the scale of the reaction, the resulting solution is subjected to a standard aqueous workup, and the product is isolated by crystallization or other purification technique known in the art. The nitro intermediate can then be reduced by methods well known in the art, preferably by hydrogenation of the corresponding nitro intermediate over a precious metal catalyst. The hydrogenation can be affected at between about 20 and about 60 psi of hydrogen, and with a variety of solvents, temperatures, and catalysts well known in the art. The reaction is preferably carried out at about 50 psi of hydrogen over 5% palladium on carbon wetted with 2B3 ethanol. The nitro intermediate is charged to the reactor along with one equivalent of acetic acid, diluted with solvent, heated to about 50°C, and subjected to hydrogen for about 5-24 hours depending on the scale of the reaction. The product is isolated as the acetic acid salt upon workup by methods well known in the art. Specific conditions for carrying out this reaction are provided in Examples 3 and 3A.

The epoxide starting material in Scheme I is prepared as shown below in Scheme IV:

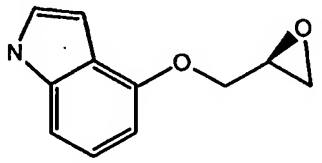
Scheme IV



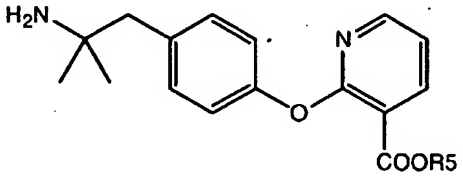
Ar in Scheme IV is as described in Structural Formula (I). Y is a sulfonate ester such as a mesylate, tosylate, *para*-nitrobenzene sulfonate or nosylate. Examples of specific conditions for this reaction are provided in Examples 2 and 2A.

Substituents which interfere with the reactions shown in the Schemes I-IV can be present, provided that they are first converted to a protected form. Suitable protecting groups are known to those skilled in the art and are disclosed in Green and Wuts, "*Protecting Groups in Organic Synthesis,*" John Wiley and Sons, 1991, the teachings of which are incorporated herein by reference.

A preferred method of preparing Compound **4** in Table 1 comprises aminating an epoxide represented by the following structural formula



with an amine represented by the following structural formula



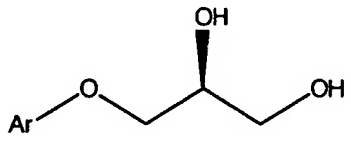
wherein R5 is methyl or ethyl, then amidating the COOR5 group with ammonia to form Compound **4**. Examples of specific

conditions for synthesizing Compound **4** according to this process are provided in Examples 9-16.

A preferred method of preparing Compound **2** in Table 1 involves first preparing Compound **6**, as shown in Scheme I, and then hydrolyzing the nitrile group to an amide. The hydrolysis reaction can be carried according to methods known in the art using, for example, polyphosphoric acid, H_2O_2 and K_2CO_3 in dimethylsulfoxide, H_2O_2 and ammonium hydroxide, H_2O_2 and sodium hydroxide, potassium hydroxide and *t*-butanol, or water and HCl.

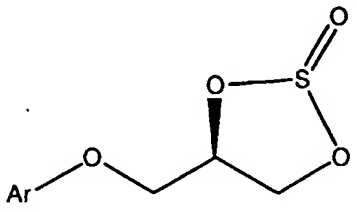
An alternative method of preparing the compounds of the present invention involves deprotecting a cyclic sulfate-containing compound to reveal hydroxy substituents, and comprises combining the cyclic sulfate-containing compound with a trialkylsilyl halide in solvent for a time sufficient to deprotect the hydroxyl group.

Specifically, the process comprises reacting a compound of the formula (XIX):



(XIX)

with thionyl halide in solvent for a time sufficient to yield a sulfite compound of the formula (XX):



(XX)

where Ar is as described above.

Suitable thionyl halides include thionyl bromide and thionyl chloride. Thionyl chloride is preferred.

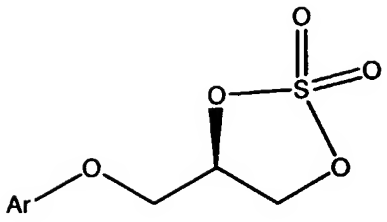
Typically, 2 equivalents of thionyl halide are used per mole of compound (XIX).

Any solvent can be used in this step, so long as it does not interfere with the reaction. THF is preferably used. The reaction is typically conducted until product is obtained, generally for about 120 to 240, preferably 180, minutes. The reaction can be conducted at any temperature, but generally is conducted at a temperature less than about 0°C, preferably from about -10 to 0 °C, more preferably from about -10 to -5°C, most preferably from about -9 to -8°C.

In some instances, especially when Ar is a heterocyclic ring, the heteroatom in the heterocyclic ring is first protected. In a preferred embodiment, R^1 is a N-containing heterocyclic ring such as benzimidazole, carbazole, imidazole, 1H-indazole, indole, isoindole, morpholine, oxazole, piperazine, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, 1,3,5-triazine, or triazole. When Ar is a N-containing heterocyclic ring, the nitrogen atom is first N-protected prior to conversion of the compound to the corresponding sulfate. Selection of the protecting group is preferably made such that it can be removed under the same conditions as for removing the sulfate group to reveal a hydroxy group.

Conditions for N-protecting the nitrogen atoms depend on the particular protecting group chosen. Suitable reaction conditions are described in "Protective Groups in Organic Synthesis," Peter G. M. Wuts (Editor), Theodora W. Greene, 3rd ed. (April 1999), Vch Pub.

Thereafter, compound (XX) can be converted into corresponding sulfate compound of the formula (XXI):



(XXI)

where Ar is as described above.

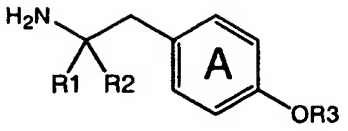
Suitably, the conversion comprises combining sulfite compound (XX) with a catalytic amount of a ruthenium compound and an oxidizing agent in solvent for a time sufficient to oxidize said sulfite compound (XX) to a sulfate compound (XXI).

Suitable ruthenium compounds include ruthenium chloride or ruthenium oxide. Generally, about 0.001 to 0.25 equivalents of ruthenium compound are used per mole of sulfite compound (XX).

Suitable oxidizing agents include sodium periodate, sodium hypochlorite, sodium bromate, calcium hypochloride, sodium chlorate or ozone. Generally, greater than about 2.0, preferably 2.5, equivalents of oxidizing agent are used per mole of sulfite compound (XX).

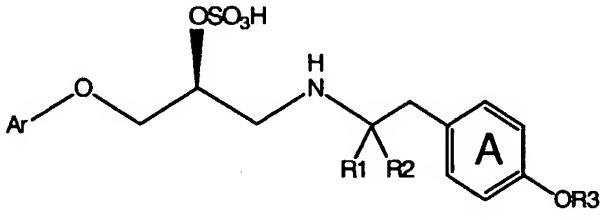
Typically the conversion is conducted in any solvent that would not interfere with the reaction, such as CCl_4, $CHCl_3$, CH_3CN, or water or mixtures thereof. The conversion is typically conducted for about 30 to 120, preferably 60, minutes. Preferably, the conversion is conducted in a mixture of $CHCl_3$, CH_3CN and water. The conversion is typically conducted at a temperature of from about -10 to 25°C.

Thereafter, the sulfate compound (XXI) can be reacted with a primary amine of the formula (XXII):



(XXII)

where R1-R3 and Ring **A** are as described above, in solvent for a time sufficient to yield a compound (XXIII):

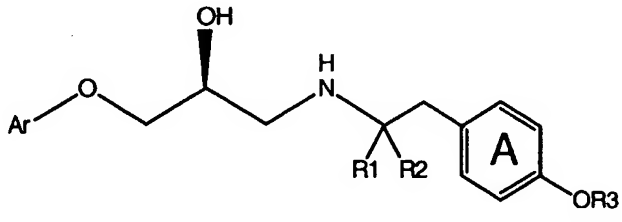


(XXIII).

Typically, about 0.9 to 2 equivalents of amine are used per mole of sulfate compound (XXI). Preferably, about 0.9 to 1.1 eq. are used. Most preferably, about 1.0 eq. (a stoichiometric amount) of amine is used.

Any solvent can typically be used in this step, as long as it does not interfere with the reaction. Preferably, the reaction is conducted in CH_3CN. The reaction is typically conducted for about 60-180, preferably 120, minutes at a temperature of from about 78 to 85°C.

Finally, the compound (XXIII) can be combined with trialkylsilyl halide in solvent for a time sufficient to yield compound (XXIV):



(XXIV)

where Ar, R1-R3, and Ring **A** are as described above.

Suitable trialkylsilyl halides include trialkylsilyl iodide, trialkylsilyl bromide or trialkylsilyl chloride. Preferably, the trialkylsilyl halide is trimethylsilyl iodide.

The reaction is conducted in any suitable solvent, so long as it does not interfere with the reaction. Preferably, the solvent is an aprotic solvent such as carbon tetrachloride, acetonitrile, dimethyl sulfoxide, dimethylformamide, sulfolane, tetrahydrofuran, diethyl ether, methyl-t-butyl ether, 1,2-dimethoxy-ethane, dioxane, chloroform, methylene chloride, toluene or acetone or mixtures thereof.

The reaction is typically conducted for 5-25, preferably 15, minutes at a temperature of less than 0°C, preferably -10 to 0°C, most preferably -9 to -8°C.

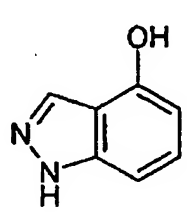
The individual optically active isomers of the compounds prepared by the present invention may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. This resolution can be carried out by derivatization with a chiral reagent followed by chromatography or by repeated crystallization. Removal of the chiral auxiliary by standard methods affords substantially optically pure isomers of the compounds of the present invention or their precursors. Further details regarding resolutions can be obtained in Jacques, et al., *Enantiomers, Racemates, and Resolutions*, John Wiley & Sons, 1981.

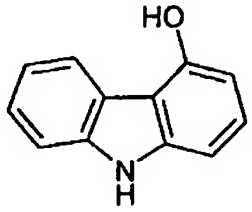
The compounds employed as initial starting materials in the synthesis of the compounds of this invention are well known and, to the extent not commercially available, are readily synthesized by standard procedures commonly employed by those of ordinary skill in the art.

The invention is illustrated by the following examples, which are not meant to be limiting in any way.

EXAMPLES

Example 1- Preparation of 4-Hydroxyindazole and 4-Hydroxycarbazole

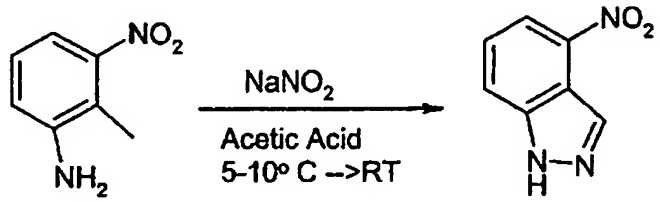




4-Hydroxycarbazole was prepared according to procedures disclosed in WO 98/09625, the entire teachings of which are incorporated herein by reference.

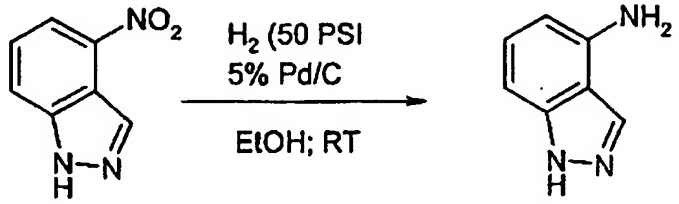
Specific conditions for preparing 4-hydroxyindazole are provided below.

A. Preparation of 4-Nitroindazole from 2-Methyl-3 Nitro-aniline



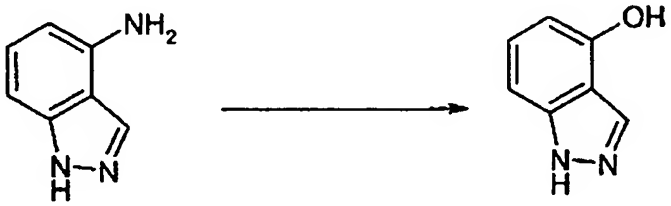
Sodium nitrite (20 grams, 0.29 mol) was dissolved in 50 mL water. This solution was added all at once to 2-methyl-3-nitroaniline (20 grams, 0.13 moles) in glacial acetic acid near zero degrees C. The reaction was stirred vigorously with an overhead stirrer. An immediate precipitate occurred upon addition of a sodium nitrite solution. The reaction was allowed to reach room temperature and stirred overnight. The precipitate was filtered off and the filtrate was concentrated *in vacuo*. The dark orange solid was suspended in water, filtered, and dried to yield 14-21 grams of a dark orange solid (99% yield).

B. Preparation of 4-Aminoindazole From 4-Nitroindazole



4-Nitroindazole (12 grams) was dissolved in ethanol (300 mL) with warming in a Parr hydrogenation vessel. A 5% palladium on carbon (12 grams) catalyst was added to the vessel. The reaction vessel was then pressurized to 50 PSI (pounds per square inch) and shaken for 1 hour. Thin layer chromatography indicated product formation and loss of starting material. The reaction mixture was filtered over Celite. The catalyst was thoroughly washed with methanol until all product was flushed off. The filtrate was concentrated to a dark gray solid, which was dissolved in ethyl acetate and filtered over a silica pad. The filtrate was concentrated to a brownish solid(9.6 grams, 97% yield).

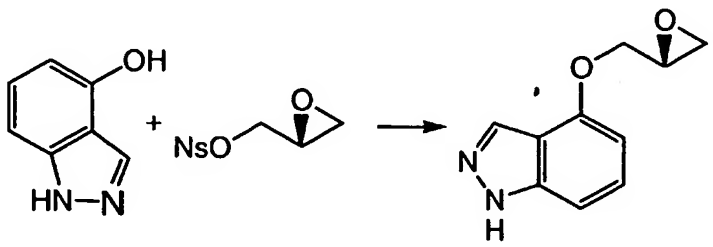
C. Preparation of 4-Hydroxyindazole From 4-Aminoindazole



4-Aminoindazole (9.6 grams, 0.072 moles) was dissolved in a glass reaction vessel containing 7.2 grams of concentrated sulfuric acid in 75 mL of water. The vessel was sealed into a stainless steel autoclave and heated to 170 degrees C overnight. The reaction mixture contained much black precipitate. The reaction mixture was diluted

with ethyl acetate and water into a separatory funnel and partitioned. The aqueous layer was extracted several times with ethyl acetate until all of the product was out of the aqueous fraction. The combined organic fractions were washed with brine, dried with magnesium sulfate, filtered, and concentrated to a dark brown or black oil. The product was purified by passing it over a silica pad with a 50% ethyl acetate/hexane mixture, resulting in an off-white solid (3.3 grams, 33% yield).

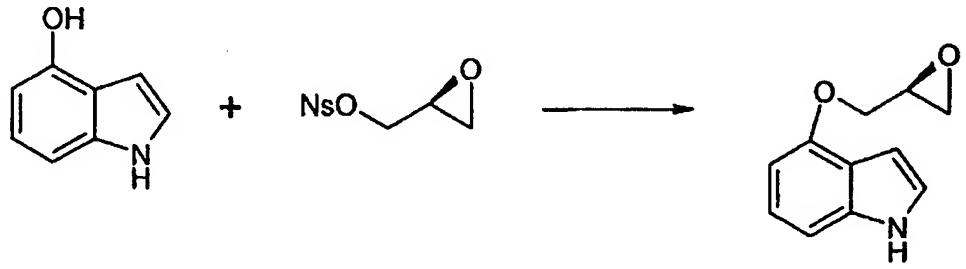
Example 2 - Preparation of (S)-Indazol-4-yloxy-1,2 Epoxypropane



Potassium carbonate (6.8 grams, 0.05 moles) was added to 4-hydroxyindazole (3.3 grams, 0.025 moles), and (2S)-(+)-glycidyl 3-nitrobenzenesulfonate (6.5 grams, 0.025 moles) in acetone at room temperature. The reaction mixture was heated to reflux for 3 hours. TLC (50% ethyl acetate/hexane) showed little starting material left, but that a bright-UV product spot appeared between the starting materials. The reaction mixture was filtered and concentrated to a dark green oil. The oil was dissolved in ethyl acetate and partitioned with water three times. The organic was dried with magnesium sulfate, filtered, and concentrated to a green oil. The oil was filtered over a silica pad with a 40% ethyl acetate/hexane mixture, resulting in a slight green oil (4.1 grams, 88%).

The product was unstable when left at room temperature or in solution for long periods of time. Thus, the product was usually stored in the freezer or used immediately in the epoxide opening reaction. Yield: 50-80%.

Example 2A - Preparation of 4 - [(2S) - Oxiranylmethoxy]-1H-indole

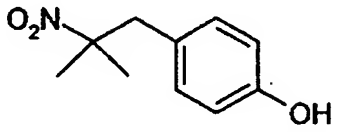


Powdered K_2CO_3 (40 grams, 289 mmol, 300 mesh) was added to dimethyl sulfoxide (DMSO) (200 mL) containing H_20 (4 mL) under N_2 at room temperature, and the mixture was stirred for 30 minutes. 4-Hydroxyindole (25.2 grams, 189 mmol) was added to the mixture (slight exotherm to 27°C), and the mixture was stirred for 10 minutes. *(S)*-Glycidyl nosylate (50.0 grams, 193 mmol, 98.5% ee) was added (slight endotherm). The slurry was stirred for 30 minutes at 20--25°C, and for 23 hours at 25-27°C until the reaction was complete. The mixture was diluted with acetone (400 mL) and filtered. The cake was washed with acetone (400 mL), and the combined filtrates were concentrated to a volume of ca. 250 mL under vacuum while maintaining the temperature below 35°C. This concentrate was added dropwise, over ca. 2 hours, to deionized H_20 (650 mL) held at a temperature of 15-20°C with an ice/water bath. The product slurry was stirred for 1 hour at this temperature and for 30 minutes at 5-10°C. The solid was isolated by filtration and washed

with cold deionized H_2O (150 mL). The solid was dried under vacuum at 35°C to yield 30.3 grams of product.

Silica Gel 62 (1.6 grams, 0.05% wt/wt) was added to a solution of the crude product above (30.3 grams, 171 mmol) in CH_2Cl_2 (100 mL) at room temperature, and the slurry was stirred for 1 hour under N_2. The mixture was then vacuum filtered and the cake was rinsed with CH_2Cl_2 (20 mL). Heptane (500 mL) was added dropwise to the filtrate over 1 hour at room temperature to precipitate the product. The resulting slurry was stirred for 30 minutes at room temperature and for 30 minutes at 0-5°C. The mixture was filtered, rinsed with cold heptane (150 mL), and vacuum-dried at 35°C/5 Torr to give 26.5 grams of product (79% yield), mp 72.4-74.0°C, which then solidified and remelted at 79.8-81.3°C.

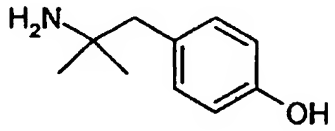
Example 3 - Preparation of 4-(2-Methyl-2-Nitropropyl) Phenol



Potassium *tert*-butoxide (29.6 grams, 264 mmol) was added to a solution of 2-nitropropane (260 mL, 2.90 mol), 4-hydroxybenzyl alcohol (65.0 grams, 524 mmol) in diglyme (260 mL) at room temperature with mechanical stirring. During the addition the reaction temperature increased from 25°C to 39°C. The reaction mixture was heated to reflux and stirred for 6 hours at ca. 137°C, using a Dean-Stark trap to remove the water as it was formed (total volume of distillate 28 mL, 7 mL aqueous phase). After cooling to room temperature, deionized H_2O (325 mL) and ethyl acetate (520 mL) were added to the reaction solution. The phases were separated and the organic phase was washed with deionized H_2O (2 x 325 mL). The organic phase was concentrated by rotary evaporation at

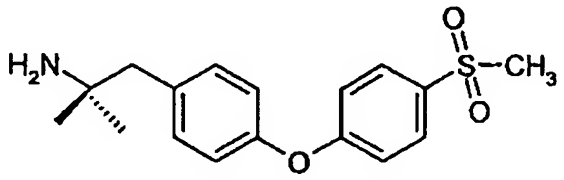
78°C to give 181.2 grams of an oil. This oil was dissolved in methanol (65 mL) for use in the next reaction. The concentration of the resulting solution was determined by ^1H NMR analysis to be 56.3% by weight (99.6% yield).

Example 3A - Preparation of the Acetate Salt of 4-(2-Amino-2-Methylpropyl)phenol



To a N_2-degassed solution of 4-(2-methyl-2 nitropropyl)phenol (45.0 grams, 230 mmol) in MeOH (450 mL) was added 5% Pd/C (13.5 grams of 50% water-wet catalyst, 15% by weight on a dry basis). The mixture was pressurized to 35-40 PSI with hydrogen and heated to 60°C with vigorous agitation. When the reaction was complete (ca. 6 hours), the mixture was cooled to room temperature and the catalyst was carefully removed by filtration through a Hy-Flow filter aid. The cake was washed with 50°C methanol (135 mL), and the combined filtrates were concentrated by rotary evaporation to a net weight of ca. 120 grams. The concentrate was diluted with ethyl acetate (500 mL), and a solution of acetic acid (14.2 grams, 235 mmol) in ethyl acetate (250 mL) was added to the resulting solution over 30 minutes. The resulting slurry was stirred for 2 hours at room temperature. The slurry was filtered and the solid washed with ethyl acetate (2 x 100 mL). The product was vacuum-dried at 65°C/5 Torr for 24 hours to give 46.5 grams (89.6%) of a white crystalline solid, mp 209-215.9 (dec).

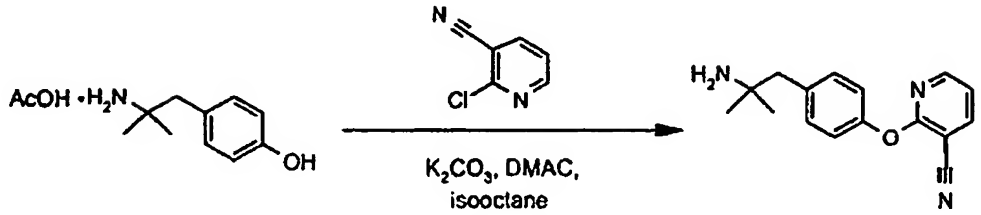
Example 4 - Preparation of (4-(2-amino-2-methylpropyl) phenoxy)-4-methylsulfonyl)benzene



A mixture of 4-(2-amino-2-methylpropyl)phenol acetic acid salt (45.06 grams, 200 mmol), powdered K_2CO_3 (69.1 30 grams, 500 mmol), 4-chloro-methylsulfonylbenzene (200 mmol), DMAC (dimethylacetamide 622 mL) and *iso*-octane (70 mL) was slowly heated to reflux at 140°C. 4-(2-Amino-2-methylpropyl) phenol acetic acid salt was prepared according to the Procedures described in Example 3 and 3A.

A water trap filled with *iso*-octane was used to collect water formed in the reaction, and reflux was maintained for 5.5 hours. The mixture was allowed to cool to room temperature, and the solids were filtered and washed with ethyl acetate. The filtrate was concentrated *in vacuo* to give a solid, which was dissolved in ethyl acetate (500 mL). To this solution were added water (800 mL), 1*N* HCl (200 mL) and methanol (50 mL). The pH of this mixture was adjusted to 7.2 with concentrated HCl, and the aqueous layer was separated and washed with methyl *t*-butyl ether (500 mL). The product was crystallized by addition of 10*N* NaOH (20 mL), which raised the pH to 11. This pH was maintained by addition of 10*N* NaOH as needed during the course of the crystallization (90 minutes). The product was filtered, washed with water, and dried *in vacuo* at 45°C to give a white solid, melting point 85.3-85.5° C. NMR was consistent with the desired product.

Example 4A - Preparation of 2-[4-(2-Amino-2 Methylpropyl) phenoxy]-3-Nitrilepyridine

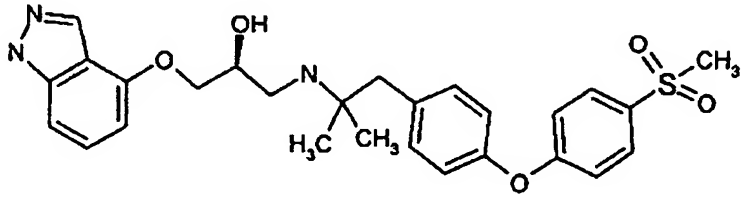


Into a 3 L three-necked flask fitted with a mechanical stirrer, Dean-Stark trap with condenser, and a thermocouple were placed the acetate salt of 4-(2-amino-2-methylpropyl)phenol (50.78 g, 0.23 mol), 2-chloronicotinonitrile (32.8 g, 0.24 mol) and powdered K_2CO_3 (77.7 g, 0.56 mol). To the solids were added N,N-dimethylacetimide (609 mL) and isooctane (2,2,4-trimethylpentane, 122 mL). The Dean-Stark trap was charged with isooctane, and the system was purged with N_2. The system was then heated to reflux with vigorous stirring and allowed to reflux for 1 hour. The olive green reaction mixture was then cooled to 30°C over one hour, and the mixture filtered through paper. The filter cake was washed with DMAC (250 mL), and the filtrate stripped at 80°C for 1.5 hours under house vacuum to yield a thick, dark green oil. The oil was taken up in dichloromethane (580 mL) and washed with deionized water (1160 mL). The layers were separated and the organic layer washed with more water (250 mL). The organic layer was then mixed with water (1 L), and the pH adjusted to approximately 1 with 25 mL of concentrated HCl. The layers were separated and the aqueous/product layer washed with dichloromethane (250 mL). The aqueous phase was then mixed with dichloromethane (1 L), and the pH adjusted to 12-13 with 5N NaOH. The layers were separated and the organic layer dried over Na_2SO_4, filtered,

and stripped to yield solid brown product (53 grams, 88%, >99% by HPLC: SB-C18 column, 40/60 isocratic mixture of acetonitrile, 0.1% TFA in water, retention time of product is 3.3 minutes).

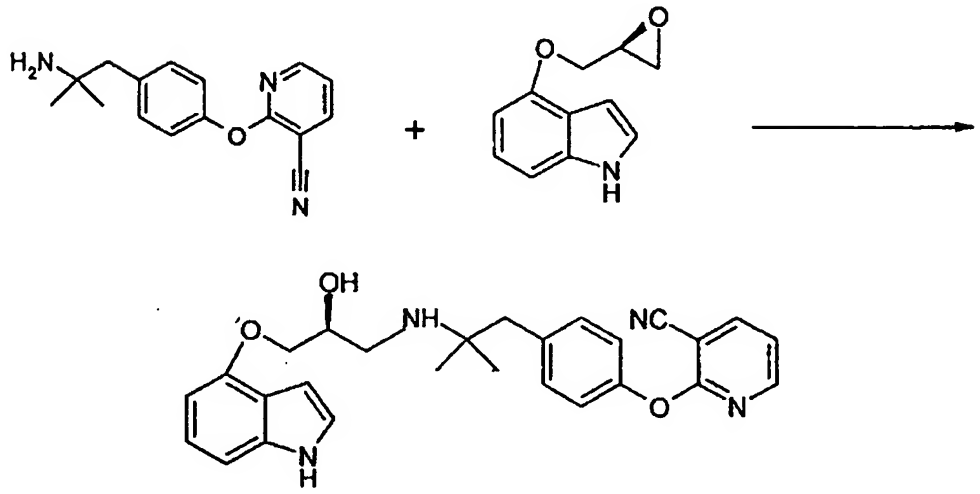
A 20 gram portion was recrystallized from toluene (60 mL) and heptane (200 mL) to provide a sample for analytical characterization, mp 91.0-94.5°C. Anal. Calcd for $C_{16}H_{17}N_3O$: C, 71.89; H, 6.41; N, 15.72. Found: C, 71.20; H, 6.38; N, 15.61.

Example 5 - Preparation of Compound 9



A stirred mixture of an (S)-3-(4-indazolyloxy)-1, 2 epoxypropane (2.5 grams, 0.013 moles), prepared as described in Example 2, and (4-(2-amino-2-methylpropyl) phenoxy)-4-(methylsulfonyl)benzene (4.5 grams, 0.014 moles), prepared as described in Example 4, in anhydrous methanol (75 mL) was refluxed for 24 hours. The reaction mixture was then concentrated *in vacuo* and purified by flash chromatography over silica (2% ammonium hydroxide, 15% methanol, 83% ethyl acetate) to give a white foam (1.8 grams, 31% yield). Compound **9** was characterized by electro-spray ionization mass spectrometry (ESIMS); the molecular ion peak was 510.0 (calculated molecular weight 509.62 amu).

Example 5A - Preparation of (S)-2-[4-[2-[2-Hydroxy-3-(1H indol-4-yloxy)propylamino]-2-methylpropyl]-phenoxy]-3-pyridinecarbonitrile, hydrochloride salt



Into a three-necked round-bottom flask fitted with a condenser, nitrogen inlet, mechanical stirrer, and a thermocouple were placed 4-[(2S)-oxiranylmethoxyl-1H-indole (8.5 grams, 44.9 mmol, 98.5% ee), 2-[4-(2-amino-2-methylpropyl) phenoxy]-3-pyridinecarbonitrile (21.01 grams, 78.6 mmol) and isopropyl alcohol (255 mL). The reaction was heated at reflux (78°C) for 17 hours under N_2. The solution was then allowed to cool to room temperature and stirred for one hour. The cooled mixture was filtered through a diatomaceous earth (HyFlo™ filtering aid (16.5 grams), and the filter cake washed with isopropanol (43 mL). The filtrate was concentrated to a net weight of 55 grams under full vacuum at 50°C. To the concentrated solution was added ethyl acetate (85 mL), and the resultant solution concentrated under the same conditions to a net weight of 52

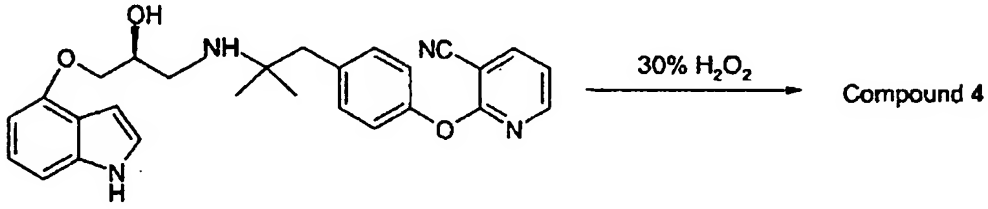
grams. The concentrate was then taken up in ethyl acetate (230 mL), and a 2.5% wt/vol NaCl solution (150 mL) was added. The biphasic system was vigorously stirred, and the pH adjusted to 7.2 with glacial acetic acid. The phases were separated and the organic phase extracted with 2.5% brine (2 x 50 mL). The organic phase was washed sequentially with NaOH/NaCl solution (50 mL, 0.89 grams NaOH) and water (50 mL).

Salt formation: The organic phase was concentrated to 40 grams net weight under the conditions noted above. The concentrate was diluted with ethyl acetate and stripped to 44.9 grams to dry the solution azeotropically. The solution was then divided into three equal portions, and one-third of the solution was concentrated to 14 grams (about 6.83 grams of free base). To the concentrate were added adequate volumes of ethyl acetate (40 mL) and ethanol (18.7 mL) to bring the solution to a ratio of 1/3.5 ethanol/ethyl acetate, taking into account residual solvent in the product concentrate, and a dilution factor of 12.3 mL/gram of product. The solution was brought to reflux and the pH was adjusted to 3.5 with a 0.5 N solution of HCl in ethyl acetate (about 30.7 mL). At this point, the solution had a ratio of approximately 1/4.3 ethanol/ethyl acetate, with a dilution factor of approximately 14.5 mL/gram of product. The solution was allowed to cool to room temperature and then stirred for 15 hours. The solution was then cooled in an ice bath and stirred at 0°C for 3 hours. The slurry was then filtered, and the crystals washed with cold 1:4 ethanol/ethyl acetate (10 mL). The product was dried overnight under vacuum at 50°C to give 5.5 grams (75%) of a white crystalline solid, mp 188.8-191.0 C. Anal. Calcd for

$C_{27}H_{29}ClN_4O_3$: C, 65.78; H, 5.93; Cl, 7.19; N, 11.36. Found: C, 65.59; H, 6.12; Cl, 7.25; N, 11.36.

The acidic aqueous extract from the workup above was adjusted to pH 12-13 with 1 N NaOH solution in a vigorously stirred biphasic system with MTBE (80 mL). The layers were separated, and the organic extract dried over Na_2SO_4, filtered, and concentrated to a solid in 80-90% yield.

Example 6 - Preparation of the free base and acetic acid salt of Compound 4 From (*S*)-2-[4-[2-[2-Hydroxy-3-(1H-indol-4-yloxy)propylamino]-2-methylpropyl]-phenoxy]-3-pyridinecarbonitrile, hydrochloride salt



Into a three-necked, round-bottom flask fitted with a nitrogen inlet, mechanical stirrer, and a thermocouple were placed (S)-2-[4-[2-[2-hydroxy-3-(1H-indol-4-yloxy) propylamino]-2-methylpropyl]phenoxy]-3-pyridinecarbonitrile, hydrochloride salt (10 grams, 20.3 mmol) and DMSO (70 mL). The reaction mixture was stirred at room temperature for 30 minutes to assure complete dissolution. The solution was placed in a cooling water bath, and 2.2 N NaOH (10 mL, 22 mmol) was added over 10 minutes while maintaining the temperature below 35°C. After stirring for 30 minutes, 30% aqueous H_2O_2 (2.71 mL) was added in seven equal portions over 40 minutes while maintaining the temperature below 35°C. The reaction was complete after 30 minutes. An aqueous solution of Na_2SO_3 (1.60 grams, 12.7 mmol in 35 mL of water) was added to the reaction mixture in 4 portions

over 15 minutes while maintaining the reaction temperature below 35°C. After 15 minutes the thick solution tested negative for peroxide. Ethyl acetate (75 mL) was added and the solution stirred for 30 minutes. Additional ethyl acetate (100 mL) and H_2O (100 mL) were added and the phases were separated. The organic phase was washed with H_2O (100 mL). The combined aqueous fractions were back- extracted with ethyl acetate (100 mL), and the organic phase combined with the earlier organic fractions. A portion of the solution (10%) was saved as a retainer of the crude free base of Compound **4**, after removal of the solvent. Compound **4** was analyzed by electro-spray ionization mass spectrometry; the molecular ion peak was 475.0 (calculated molecular weight was 474.56).

The remainder of the combined organic extracts was concentrated by rotary evaporation at 50°C to a net weight of 18-20 grams. The residue was dissolved in ethyl acetate and ethanol to give a 7:1 ratio of ethyl acetate/ethanol with a concentration of 8 mL/grams of free base. The percent water was determined by Karl Fischer titration. The water content should be between 1.0-2.0 % w/w for maximum yields in the crystallization. After the solution was heated to reflux, glacial acetic acid (1.10 grams, 18.3 mmol) was added and the solution was seeded. The slurry was cooled to room temperature and stirred overnight. After cooling at 0°C for 2 hours, the product was filtered, the cake was washed with cold 7:1 ethyl acetate/ethanol (20 mL), and the solid was air-dried for 1 hour. The product was vacuum-dried overnight at 70°C to give 7.4 grams (96% purity, 86% yield) of product as a white crystalline solid, mp 137 °C, (shrinks) 143.1-153.2°C. Anal. Calcd for $C_{27}H_{30}N_4O_4$

• $C_2H_4O_2$: C, 65.15; H, 6.41; N, 10.48. Found: C, 65.55; H, 6.37; N, 10.88.

Hydrochloride Salt

A solution of HCl in ethanol (7.04 mL of a 0.6 M solution, 4.22 mmol) was added to a refluxing solution of the Compound **4** freebase (2.0 grams, 4.2 mmol) in ethanol (9.0 mL). The pH was carefully adjusted to 3.0, adding triethylamine or HCl as required. The solution was seeded and allowed to cool to room temperature, at which point it was stirred overnight. The slurry was cooled to 0°C for 2 hours and filtered. The filtrate was washed with 3 mL of cold ethanol. The off-white solid was vacuum dried overnight at 50°C/5 Torr to give 1.90 grams (88% yield) of an off-white solid, mp 207.0-211.0 °C. Anal. Calcd for $C_{27},H_{30}N_4O_4$ • HCl: C, 63.46; H, 6.11; N, 10.96. Found: C, 63.00; H, 6.19; N, 11.04.

Other lots prepared by a similar process were shown to be crystalline solids by x-ray powder diffraction.

The 4-Hydroxybenzoate Salt

A solution of 4-hydroxybenzoic acid (12.53 grams, 90.7 mmol) in hot ethanol (171 mL) was added to a refluxing solution of the freebase of Compound **4** (42.8 grams, 90.2 mmol) in ethyl acetate (343 mL), and the resulting solution refluxed for 15 minutes. The solution was decanted away from a small amount of insoluble residue and seeded. The solution was cooled slowly to room temperature and stirred overnight. The slurry was cooled to 0°C for 2 hours. The solids were filtered, washed with cold 2:1 ethyl acetate/ethanol, and vacuum-dried overnight at 70°C/5 Torr to give 45.4 grams (82% yield) of an off-white solid, mp

148.3-150.5 °C, which solidified and remelted at 159-186.9°C (dec). Both the wet cake and the dried solid were shown to be crystalline by X-ray powder diffraction.

Oxalate Salt

A hot solution of oxalic acid (37.8 mg, 0.42 mmol) in methanol (2.5 mL) was added to a refluxing solution of the freebase of Compound **4** (250 mg, 0.53 mmol) in methanol (2.5 mL). The solution was heated at reflux for 1 hour. The solution was cooled slowly to room temperature and stirred overnight. The slurry was cooled to 0°C for 2 hours. The solids were filtered, washed with cold methanol, and dried overnight at 70°C/5 Torr to give 194 mg (65%) of an off-white solid, mp 214.9 °C (dec). Both the wet cake and the dried solid were shown to be crystalline by X-ray powder diffraction.

Example 7 - Preparation of other Compounds of the Present Invention

Other compounds of the present invention were prepared by reacting the appropriate (S)-3-(aryloxy)-1,2-epoxypropane with the appropriate amine starting material according to the procedures described above.

The amine starting materials were prepared according to procedures described in Example 4 using the appropriately substituted chlorobenzene or chloropyridine (e.g., 6-chloronicotinamide for Compounds **1** and **2**; 2-chloronicotinamide for Compounds **3** and **4**; 2-chloro-5-cyano-pyridine for Compounds **5** and **6**; and *N*-(6-chloro-3-pyridylcarbonyl) morpholine for Compounds **7** and **8**). *N*-(6-chloro-3-pyridylcarbonyl) morpholine was prepared by reacting 6-chloro-3-pyridylcarboxylic acid with thionyl

chloride to form the corresponding acid chloride, and then amidating with morpholine.

4-Hydroxycarbazole was prepared according to procedures described in WO 98/09625, the entire teachings of which are incorporated herein by reference.

Aryloxy propanolamines with a benzimidazolone or benzimidthioazolone moiety (e.g., Compounds **12-17**) were prepared according to procedures described in U.S. Patent Nos. 5,808,080 and 5,840,738 for the preparation of Compounds **11** and **60**, using the appropriate amine as a starting material in place of 6-chloronicotinamide. The entire teachings of U.S. Patent No. 5,808,080 and 5,840,738 are incorporated herein by reference.

The compounds were characterized by electro spray ionization mass spectometry or by FD mass spectometry, the results of which are shown in Table 1.

Example 8 - Preparation of the Glycolate Salt of Compound **2**

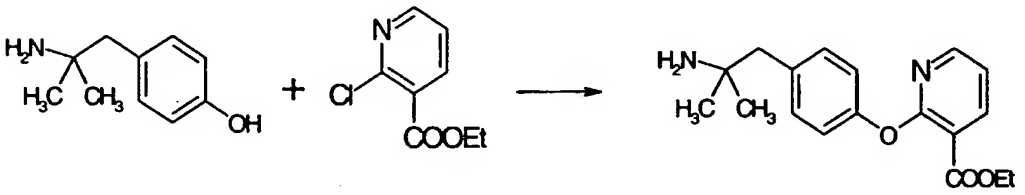
Compound **2** (500 mg, about 1 mmol) was dissolved in 3.0 ml of absolute ethanol with warming to 35-40°C. A solution of glycolic acid (0.076 g, 1 mmol) dissolved in 1.0 ml of ethanol was added to the reaction mixture with a 1.0 ml ethanol rinse in. Crystallization began as the addition finished. The mixture was stirred at 38-40°C for 90 minutes. The heat was turned off and stirring continued 90 minutes at ambient temperature. The crystals were filtered and washed with 3.5 ml of ethanol. This large volume of wash was needed to remove the crystals from the flask. Less may be used on a larger scale. After vacuum drying at 55 °C for 18 hours and without heat for two days, 1.1% ethanol was shown to remain by NMR. m.p. = 171-172°C. Yield was an

estimated 90% uncorrected for solvents. HPLC analysis gave an uncorrected purity >99%.

HPLC analysis was conducted as follows: Gradient system Solvent A: ACN; Solvent B: pH 2 phosphate buffer (1.0 liter DI H_2O, 1.0 g KH_2PO_4, 3.0 ml conc. H_3PO_4). Gradient curve: 20%A/80%B to 80%A/20%B over 20 min. Flow rate: 2 ml/min. Column: Zorbax RX C18, 4.6 x 250 mm, heated to 40°C. UV detector wavelength: 240 nm.

^1H NMR and ^{13}C NMR were consistent with the formation of the desired product. MS(FIA) *m/z* 475.

Example 9 - Synthesis of 2-[4-(2-amino-2-methylpropyl)phenoxy]-3-pyridinecarboxylic acid, ethyl ester.



4-(2-Amino-2-methylpropyl)phenol (55.18 grams, 244.9 mmol) was added to 5.05 N KOH (97.2 mmol, 2.0 equiv). The mixture was warmed to 50 °C to give a homogeneous yellow solution. Chlorobenzene (1104 mL) and N,N-dimethylacetamide (10.7 grams, 122 mmol) were added and the mixture was heated to reflux (ca. 100 °C). The water was removed azeotropically via a Dean-Stark trap. At ca. 125 °C a solid began to form. When the pot temperature reached 132 °C the water had been removed and the reaction mixture was a thick but stirrable slurry (mechanical stirring required). The Dean-Stark trap was removed and an additional 100 mL of chlorobenzene was removed and discarded. Dry chlorobenzene (50 mL) was added to the slurry, followed by ethyl 2-chloronicotinate (50.0 grams, 269 mmol) in chlorobenzene (50 mL). The slurry was

heated at reflux until the reaction was complete (ca. 24 hours). As the reaction progressed the slurry thinned and became beige in color. After cooling to room temperature, water (385 mL) and 1 N NaOH (25 mL, 0.1 equiv) were added to the mixture and the phases were separated. The organic phase was washed with water (285 mL) and the solution was concentrated to a net weight of 700 grams (9.83% potency by HPLC, 89% yield) for use in the next reaction.

Example 10 - Preparation of 2-[4-(2-amino-2-methylpropyl)phenoxy]-3-pyridinecarboxylic acid, ethyl ester, acetic acid salt.

Ethyl 2-[4-(2-amino-2-methylpropyl)phenoxy]-3-pyridinecarboxylate (10.3 grams, 32.8 mmol) was dissolved in ethyl acetate (52 mL) and heptane (41 mL) and the solution was heated to reflux. Acetic acid (1.97 grams, 38.8 mmol) was added, the solution was seeded, and cooled slowly to room temperature. After 30 minutes at room temperature, the slurry was cooled to 0 °C and stirred for 1.5 hours. The product was filtered, washed with cold 1:1 ethyl acetate/heptane (20 mL), and vacuum-dried at 50 °C for 18 hours to give 10.29 g (97% purity, 81% yield), mp 122.9-124.5 °C.

Example 11 - Preparation of (*S*)-2-[4-[2-[2-Hydroxy-3-(1*H*-indol-4-yloxy)propylamino]-2-methylpropyl]-phenoxy]-3-pyridinecarboxylic acid, ethyl ester, 4-hydroxybenzoic acid salt

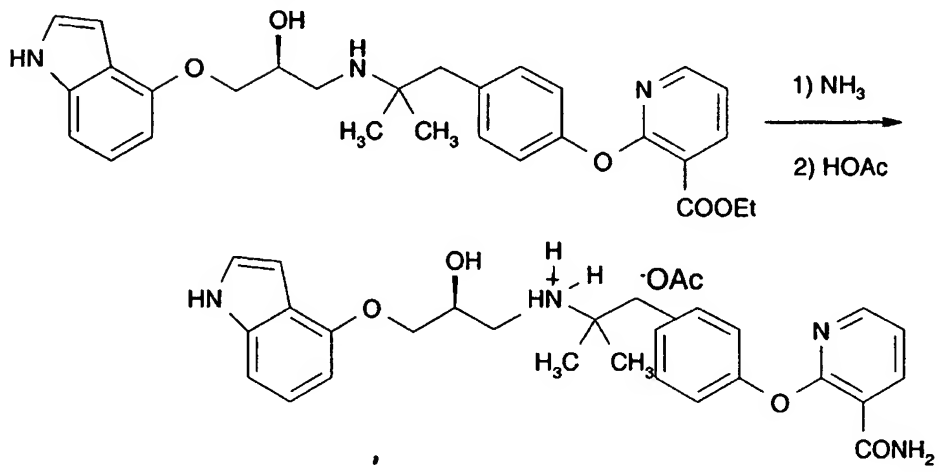
4-[(2S)-Oxiranylmethoxy]-1H-indole (9.00 grams, 47.6 mmol) was added to a solution of ethyl 2-[4-(2-amino-2-methylpropyl)-phenoxy]-3-pyridinecarboxylate (162.8 grams of a 10.1% w/w solution in chlorobenzene, 52.3 mmol) and the

resulting solution was heated at reflux for 37 hours. When the epoxide had been consumed, the solution was cooled to 80 °C, and a 50 °C solution of 4-hydroxybenzoic acid (6.57 grams, 47.6 mmol) in 2B-3 ethanol (34 grams) was added in one portion. The homogeneous solution was seeded at 70 °C and cooled slowly to room temperature with stirring. After stirring for 1 hour at 0 °C the slurry was filtered, washed with chlorobenzene (3 x 50 mL), and vacuum-dried at 70 °C for 18 hours to give 20.82 grams (68% yield) of product as an off-white solid, mp 172.4-175 °C. Anal. Calcd for $C_{29}H_{33}N_3O_5 \cdot C_7H_6O_3$: C, 67.38; H, 6.12; N, 6.54. Found: C, 67.18; H, 6.07; N, 6.77.

Example 12 - Preparation of (*S*)-2-[4-[2-[2-Hydroxy-3-(1*H*-indol-4-yloxy)propylamino]-2-methylpropyl]-phenoxy]-3-pyridinecarboxylic acid, ethyl ester

The 4-hydroxybenzoic acid salt of the title compound (17.1 grams, 26.6 mmol) was added with stirring to a mixture of methyl *tert*-butyl ether (200 mL, MTBE) and 1 N NaOH (75 mL). When all of the initial solid was dissolved a small amount of a dark green solid remained which was easily removed by filtration (Whatman #1 paper). The organic phase was washed with brine (2 x 30 mL) and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration. The MTBE solvent was exchanged with methanol by concentrating the solution using rotary evaporation, redissolving the residue in MeOH, and reconcentrating again. This process was repeated and the residue was dissolved in anhydrous methanol and used directly in the subsequent reactions.

Example 13 - Preparation of (*S*)-2-[4-[2-[2-Hydroxy-3-(1*H*-indol-4-yloxy)propylamino]-2-methylpropyl]-phenoxy]-3-pyridinecarboxamide, acetic acid salt



A solution of ethyl (*S*)-2-[4-[2-[2-hydroxy-3-(1*H*-indol-4-yloxy)propylamino]-2-methylpropyl]-phenoxy]-3-pyridinecarboxylate (13.2 grams, 26.1 mmol) in methanol (66 mL) was poured into a vessel that was then pressurized and vented 3 times with 25 psig (pounds per square inch gauge) ammonia. The internal vessel pressure was then brought to 50 psig with ammonia and the yellow solution stirred at 24 °C for 18 hours. The solvent and ammonia were removed by rotary evaporation until 25 grams remained in the flask. Ethanol (100 mL, 2B-3) was added and the solvent again removed by rotary evaporation until 26 grams remained. This addition of ethanol and evaporation was repeated 3 more times for the solvent exchange into ethanol and removal of ammonia. After the last evaporation, the contents of the flask weighed 25.0 grams and was taken to be the theoretical 12.5 g of freebase and 12.5 grams of ethanol. Ethyl acetate

(87.7 mL) and H_2O (1.0 mL) were added and the solution was brought to reflux. Acetic acid (1.73 grams, 28.8 mmol) was added and the solution was seeded. After 1 hour, heating was removed from the white mixture. After stirring at 24 °C for 1 hour, the white solid was collected by vacuum-filtration and washed twice with 7:1, ethyl acetate:ethanol (20 mL) and once with 7:1 ethyl acetate:ethanol (10 mL). Vacuum drying overnight at 50 °C/5 Torr gave 11.6 g (96.9% purity, 97% yield) as a white solid, mp 157-158 °C. Anal. Calcd for $C_{27}H_{30}N_4O_4$: C, 65.15; H, 6.41; N, 10.48. Found: C, 65.01; H, 6.28; N, 10.26.

Example 14 - Preparation of (*S*)-2-[4-[2-[2-Hydroxy-3-(1*H*-indol-4-yloxy)propylamino]-2-methylpropyl]-phenoxy]-3-pyridinecarboxylic acid, ethyl ester, 4-hydroxybenzoic acid salt

4-[(2S)-Oxiranylmethoxy]-1H-indole (8.00 grams, 42.3 mmol was added to ethyl 2-[4-(2-amino-2-methylpropyl)-phenoxy]-3-pyridinecarboxylate (14.4 grams, 46.5 mmol) in 2B-3 ethanol (80 mL) and the resulting solution was heated at reflux for 20 hours until the epoxide had been consumed. The solution was cooled to 70-75 °C, and a 70-75 °C solution of 4-hydroxybenzoic acid (5.9 grams, 42.3 mmol) in 2B-3 ethanol (20 mL) was added in one portion. The homogeneous solution was seeded and stirring continued at 70-75 °C for 1 hour. The mixture was cooled to 26 °C and stirred for 1 hour, then cooled to 5 °C and stirred for an additional hour. The solid was collected by filtration, washed with 2B-3 ethanol (45 mL), and vacuum-dried at 50 °C for 45 hours to give 21.8 grams (80.4% yield) of product as an off-white solid, mp 174-176 °C.

Example 15 - Preparation of (*S*)-2-[4-[2-[2-Hydroxy-3-(1*H*-indol-4-yloxy)propylamino]-2-methylpropyl]-phenoxy]-3-pyridinecarboxylic acid, ethyl ester

To the 4-hydroxybenzoic acid salt of the title compound (40.0 grams, 62.3 mmol) were added with stirring methyl *tert*-butyl ether (350 mL, MTBE) and methyl alcohol (20 mL). Stirring was continued for 90 minutes until the solid was well dispersed, then 1N sodium hydroxide (160 mL) and deionized water (40 mL) were added. Once the solid was dissolved the layers were separated, and the organic phase was extracted twice with a solution of deionized water (120 mL) and sodium chloride (8.0 g). After cooling to 0-5 °C and filtering through glass paper the organic layer was concentrated to 80 mL at 40 °C and 24-28 inches Hg. Methyl alcohol (160 mL) was added and the volume again reduced to 80 mL. The total volume was brought back to 240 mL with methyl alcohol and this solution was used directly in the subsequent reactions.

Example 16- Preparation of (*S*)-2-[4-[2-[2-Hydroxy-3-(1*H*-indol-4-yloxy)propylamino]-2-methylpropyl]-phenoxy]-3-pyridinecarboxamide, acetic acid salt

A solution of ethyl (*S*)-2-[4-[2-[2-hydroxy-3-(1*H*-indol-4-yloxy)propylamino]-2-methylpropyl]-phenoxy]-3-pyridinecarboxylate (31.4 grams, 62.3 mmol) in methyl alcohol (264 mL) was pressurized and vented 3 times with 5 psig ammonia. The internal vessel pressure was then brought to 5 psig with ammonia and the yellow solution stirred at 40 °C for 22 hours. The volume was concentrated to 60 mL at 30-40 °C and 25 inches Hg. Methyl ethyl ketone (450 mL,

MEK) was added and the volume reduced to 60 mL at 40-50 °C and 25 inches Hg. MEK was again added (200 mL) and the volume reduced to 60 mL. At 15-20 °C the contents were brought back to a total volume 300 mL using MEK, filtered using a 20 micron fritted glass filter funnel, then rinsed with MEK to give a total filtrate volume of 310 mL. The solution was heated to 65 °C and a solution of glacial acetic acid (3.75 g, 62.4 mmol) in MEK (15 mL) at 65 °C was added. After seeding the mixture was stirred at 65 °C for 90 minutes, then allowed to cool to 25 °C with stirring over 14 hours. The mixture was cooled to 3 °C and stirred for 1 hour. The slurry was collected by filtration, washed with MEK (90 mL), and vacuum-dried at 70 °C for 46 hours to give 30.3 grams (90.9% yield) of product as an off-white solid, mp 156-158 °C.

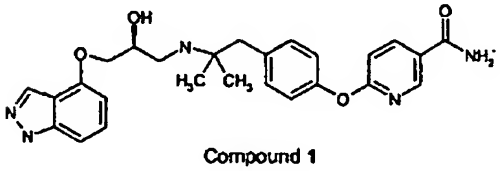
Example 17 - Intravenous Administration of the Compounds of the Present Invention to Cattle

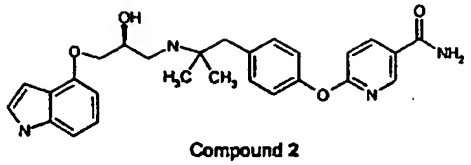
Intravenous administration of the aryloxy propanolamines compounds of the present invention to cattle was found to decrease the level of serum urea nitrogen in the cattle. Angus/Angus-cross calves, both heifers and steers, weighing approximately 282 pounds (128 kg) initially to 788 pounds (358 kg) over the course of these studies, were placed in pens at 5 calves per pen. Calves were fed *ad libitum* twice daily, (approximately 6-15 pounds/day). During the treatment day, in the A.M. period, the feeding times were staggered to ensure that all animals were fed approximately one hour before the treatments were administered. During the P.M. treatment period, the cattle were fed immediately after receiving the P.M. injection.

After taking a pretreatment (T=0) blood sample from each animal, a 40 μg per kilogram dose of a test compound was administered intravenously in the jugular vein at 6:30 A.M. and 2:30 P.M. Each test compound was administered at a concentration of 1.00 - 1.25 mg/ml in a treatment vehicle that was a 50/50 mixture of polyethylene glycol 200/water.

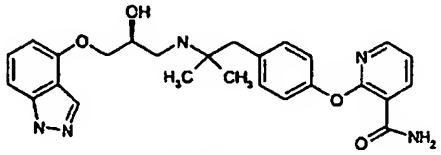
A blood sample was taken at fifteen minutes post-treatment (T+15 min). The calves were returned to their respective pens until their next treatment, approximately eight hours later. The next morning at 6:30 A.M. a blood sample was collected from all calves at 24 hours post-treatment (T +24h). All blood samples were analyzed for the serum urea nitrogen level (SUN). The post-treatment SUN levels in each individual animal were compared with the levels found before treatment. The results are shown in Table 1.

Table 1

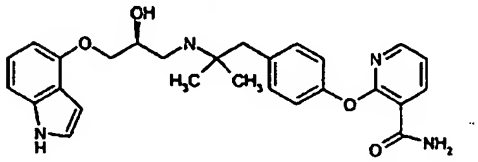
STRUCTURE	Δ%SUN* 24 Hours	Molecular Ion Peak from ES Mass Spec.
Vehicle only	~0	
 Compound 1	-28.7	476.2



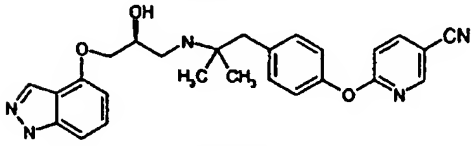
Compound 2 -22.6 475.2



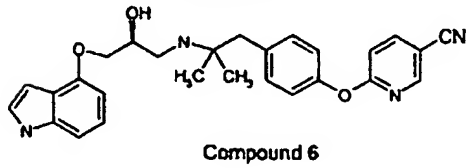
Compound 3 -39.3 476.0



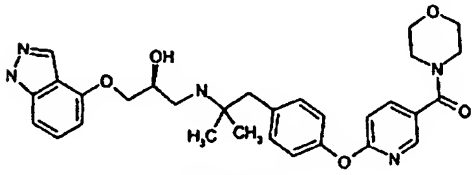
Compound 4 -47.0 475.0



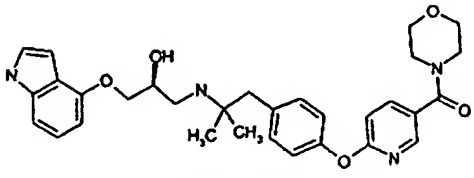
Compound 5 -24.7 458.0



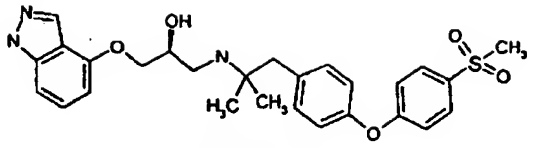
Compound 6 -56.9 475.2



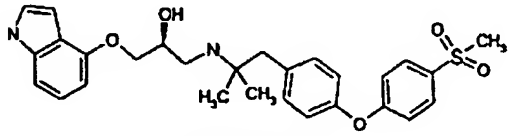
Compound 7 -40.1 546.0



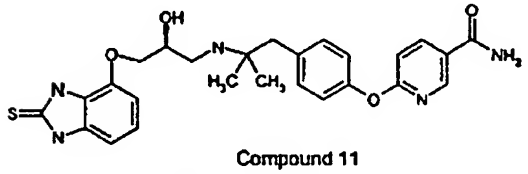
Compound 8 -38.3 545.4



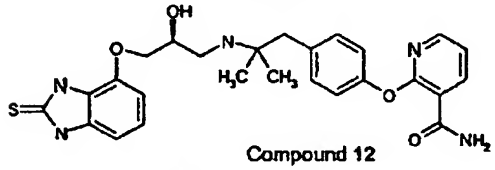
Compound 9 -25.4 510.0



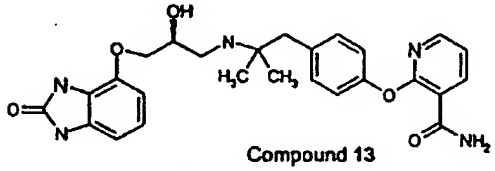
Compound 10 -38.6 509.25



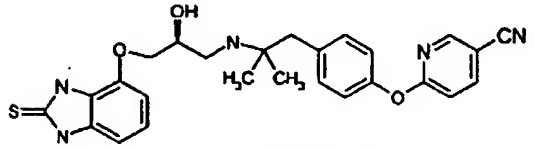
Compound 11 -38.2 508.0



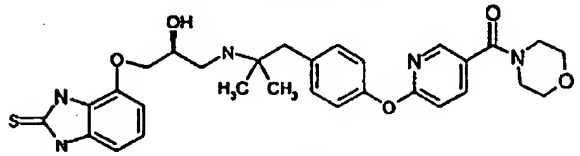
Compound 12 -57 508.0



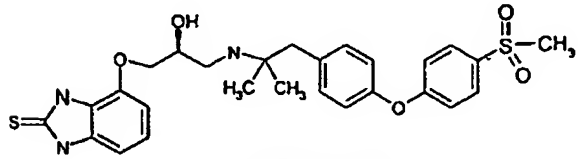
Compound 13 -14.2 492.24



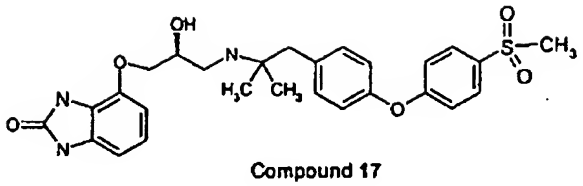
Compound 14 -54.3 490.0



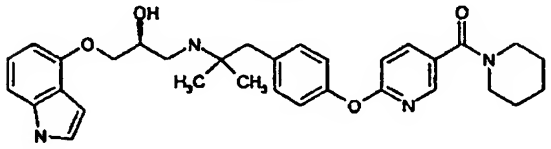
Compound 15 -55.5 578.0



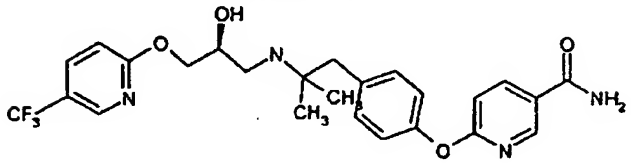
Compound 16 -54.1 542.0



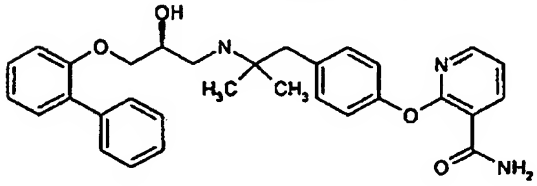
Compound 17 -28.4 526.2



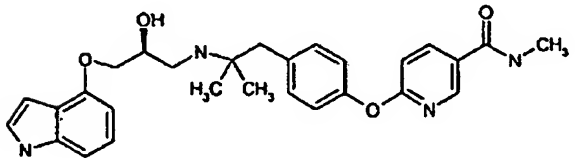
Compound 18 -38.2 543.0



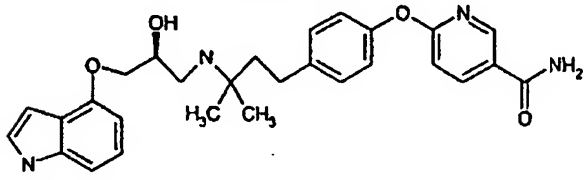
Compound 19 -1.9 505.0



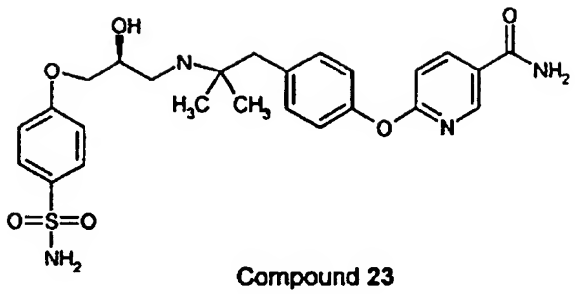
Compound 20 -9.3 512.0



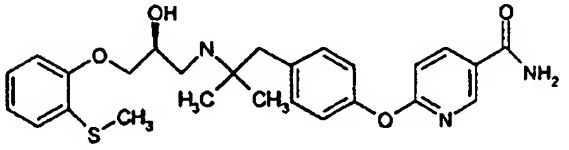
Compound 21 -31.3 489.0



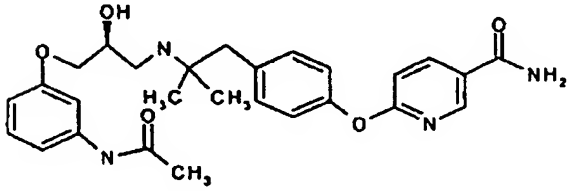
Compound 22 -24.8 489.4



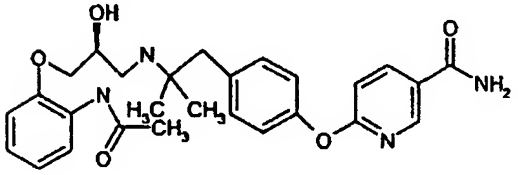
Compound 23 -1.6 515.5



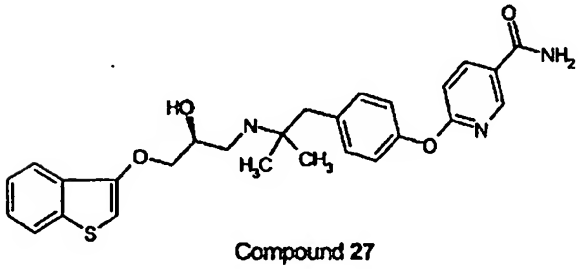
Compound 24 -7.7 482.4



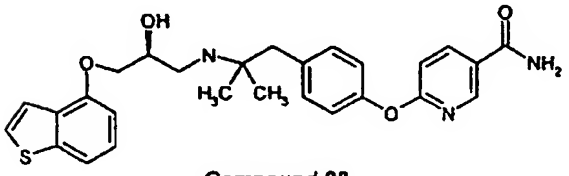
Compound 25 -4.4 493.3



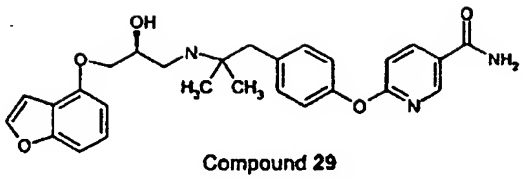
Compound 26 -2.5 493.4



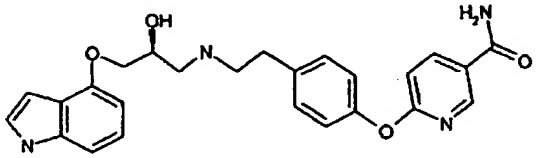
Compound 27 1.7 492.0



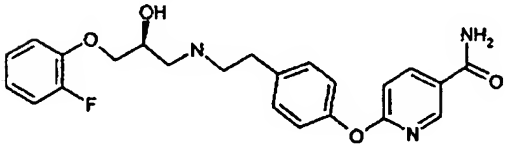
Compound 28 -1.4 491.2



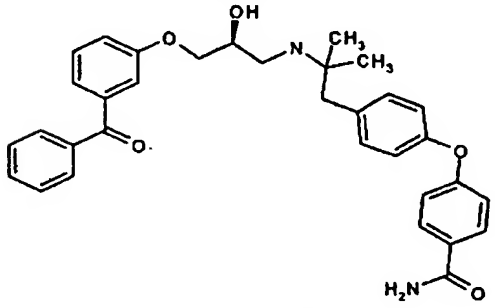
Compound 29 -3.0 476.2



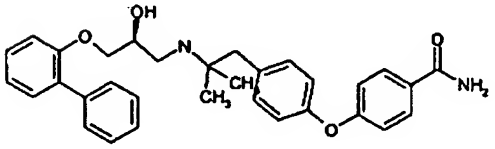
Compound 30 -19.7 447



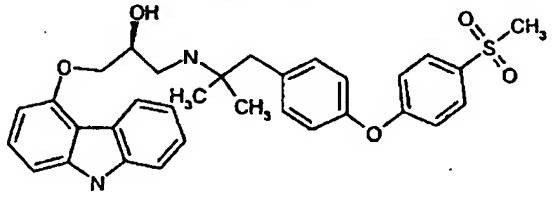
Compound 31 -7.7 426.1



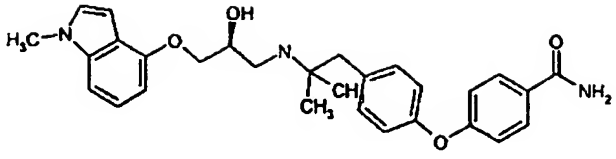
Compound 32 -8.3 538.9



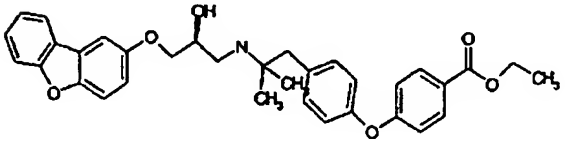
Compound 33 -18.2 511.0



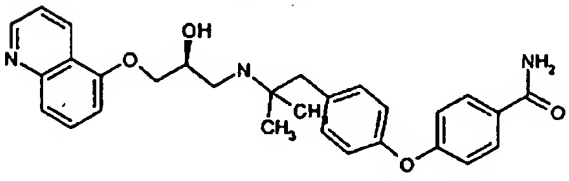
Compound 34 -8.8 559.0



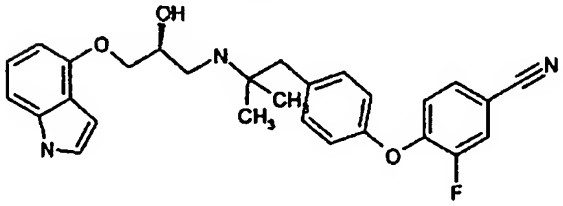
Compound 35 -26.3 487.2



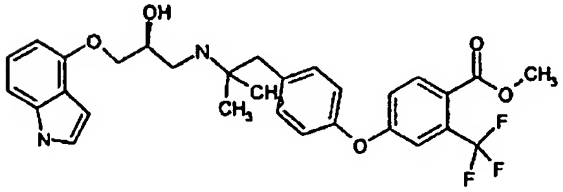
Compound 36 0.8 554.0



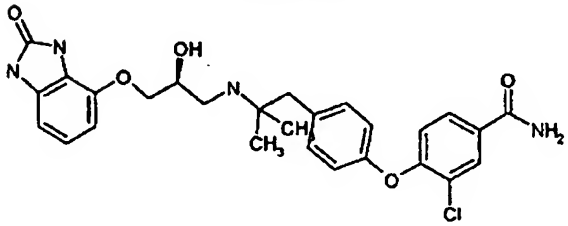
Compound 37 -17.2 ---



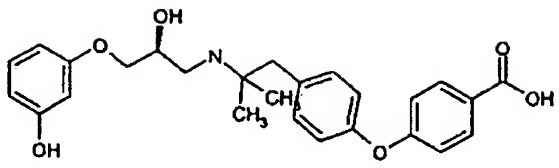
Compound 38 -26.15 474.2



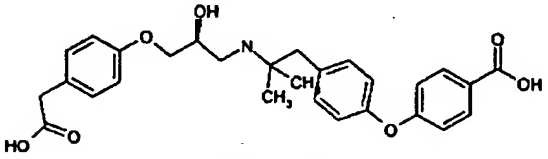
Compound 39 -18.5 556.8



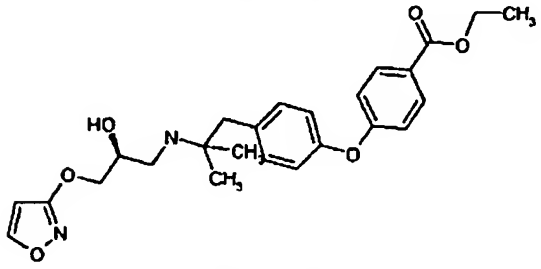
Comp und 40 -9.6 499.3



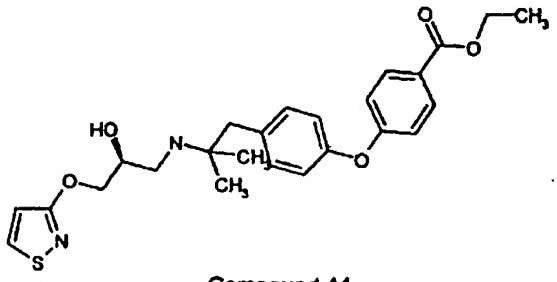
Compound 41 -12.4 452.0



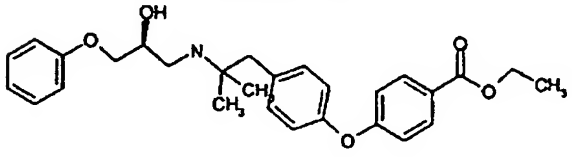
Compound 42 0.98 266.0



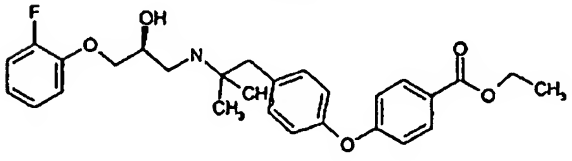
Compound 43 0 ---



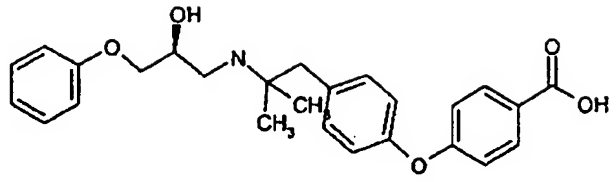
Compound 44 5.9 ---



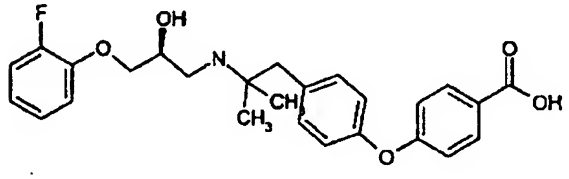
Compound 45 -7.7 464.2



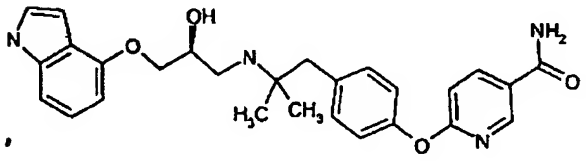
Comopund 46 -16.8 482.0



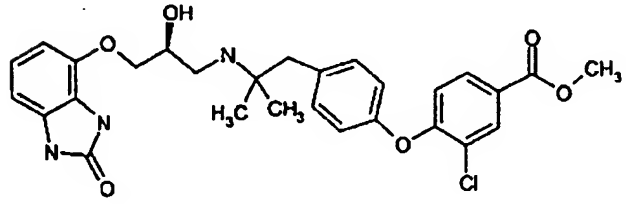
Compound 47 -9.7 ---



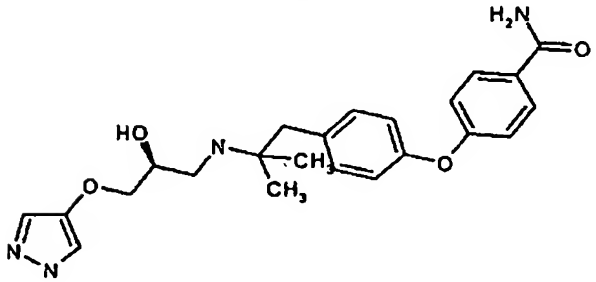
Compound 48 -12.8 ---



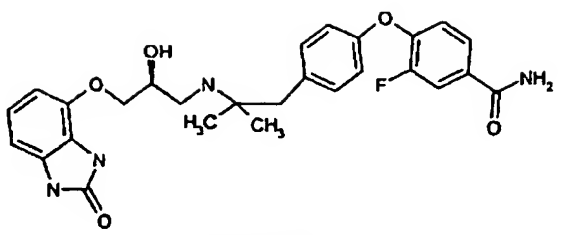
Compound 49 -28.6 475.2



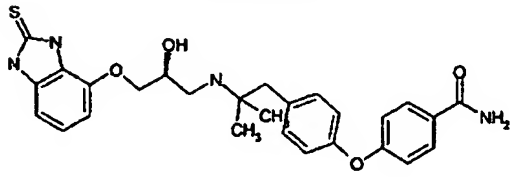
Compound 50 -27.2 539.2**



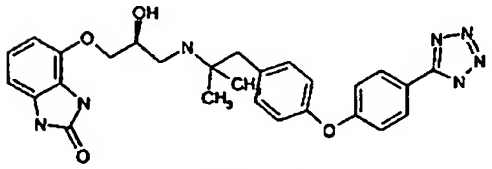
Compound 51 -9.7 425.2**



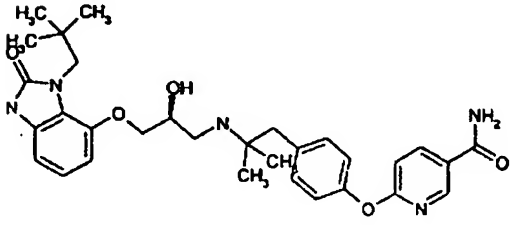
Compound 52 -18.4 508.8**



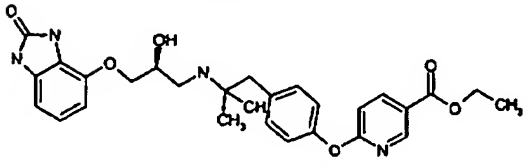
Compound 53 -42.0 507.0**



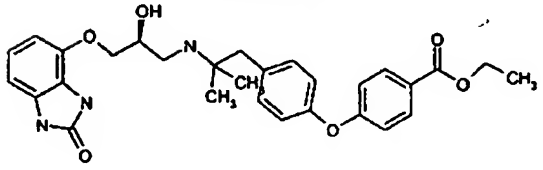
Compound 54 -8.3 515.9**



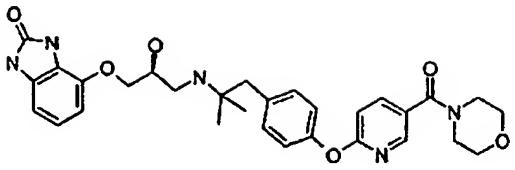
Compound 55 -5.9 ---



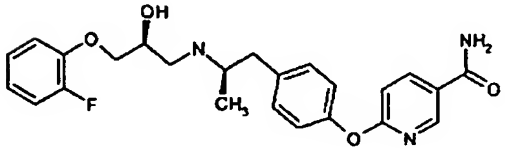
Compound 56 -10.4 520.07



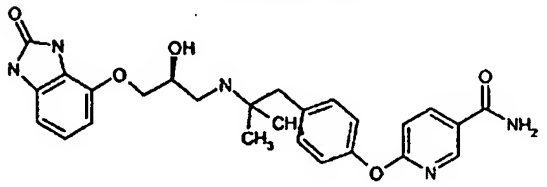
Compound 57 -39.9 520.0**



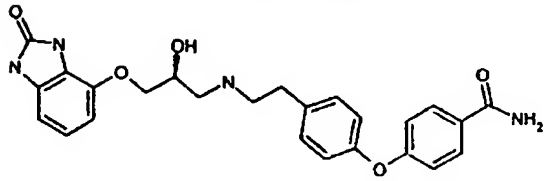
Compound 58 -22.1 562.1**



Compound 59 -35.3 439.8**



Compound 60 -9.7 492.1



Compound 61 -15.5 463.0

* The percent decrease in SUN in the blood of animals treated with the indicated test compound at 24 hours post treatment compared with the baseline (T=0) SUN value for each individual. Values presented are the mean of five animals.

$$\%\Delta SUN = \frac{(T+24h\ SUN) - (T=0\ SUN)}{T=0\ SUN} \times 100\%$$

** Indicates FD Mass Spec

A decrease in SUN is indicative of anabolic activity. The larger the percent decrease in SUN, the larger the anabolic activity.

Example 18 - Oral Administration of The Compounds of the Present Invention to Cattle

The aryloxy propanolamine compounds of the present invention were found to have anabolic activity when administered orally to cattle. Fifteen head of Angus/Angus-cross steer calves, weighing approximately 484 pounds (220 kg) initially to 604 pounds (274 kg) by the end of these three trials, were placed in pens in the cattle facilities, at 5 calves per pen. Standard vaccination and coccidal controls were administered.

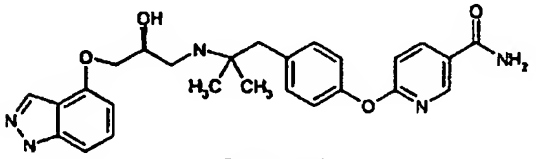
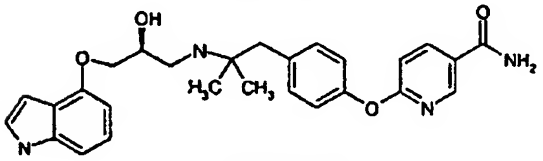
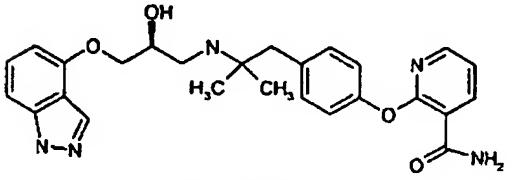
Calves were fed *ad libitium* twice daily, approximately 10-15 pounds (4.54-6.81 kg)/day. The feeding times were staggered once treatment was initiated to ensure that all calves were fed approximately one hour before the treatments were administered and blood samples obtained. During the A.M. treatment period, the cattle were prevented from returning to feed until the +180 minute blood sample had been collected.

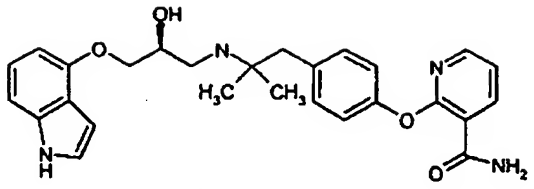
Treatments were administered once a day via oral gavage. The treatments contained 1 mg of test compound per kilogram body weight, and were administered in a 50/50 PEG 200/water vehicle, followed with a flush of 20 mls of 50/50 PEG 200/water.

A baseline blood sample (T=0) was taken immediately before the oral gavage treatment was administered. At 90 minutes post-treatment (T+90 min) another blood sample was taken. The cattle were returned to their designated pens until 180 minutes post-treatment (T+180 min), when a third blood sample was collected. The calves were not allowed access to their feed until they had completed the 180 minute blood sample. Additional blood samples were collected from each calf at 24 and 48 hours post-treatment.

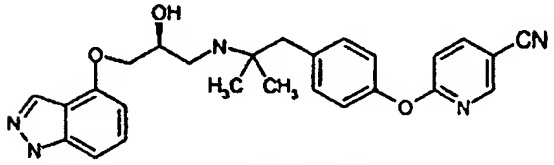
All blood samples were taken from the jugular vein and placed into serum tubes. Serum was assayed on an IL Monarch analyzer. Blood samples were collected pretreatment (T=0), 90 minutes post-treatment (T+90 min), 180 minutes post-treatment (T+180 min), 24 hours post-treatment (T+24h), and 48 hours post-treatment (T+48h). Sera at T=0, T+90min, T+180 min, T+24h, and T+48h were analyzed for serum urea nitrogen. The results at T+24h and T+48h are shown below in Table 2.

Table 2

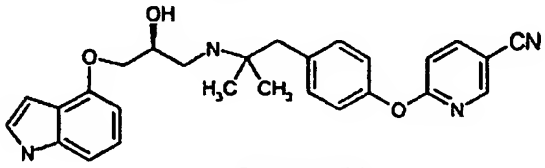
STRUCTURE	Δ%SUN* 24 Hours	Δ%SUN** 48 Hours
Vehicle only	~0	~0
 Compound 1	-38	-32
 Compound 2	-24.5	-16.1
 Compound 3	-56	-57



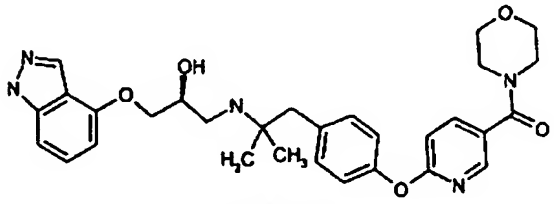
Compound 4 -42 -30



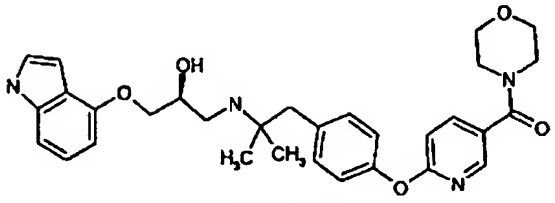
Compound 5 -58 -57



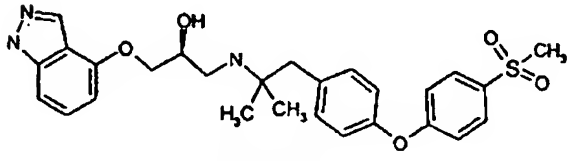
57 Compound 6 -55, -40



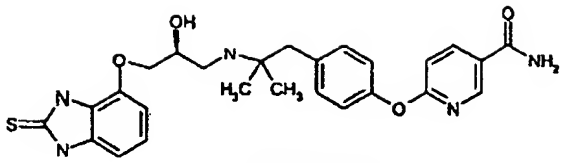
40 Compound 7 -47 -48



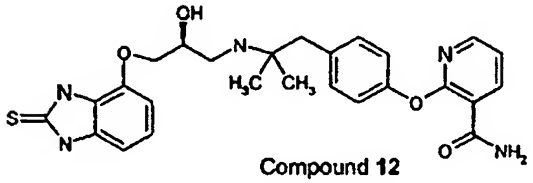
Compound 8 -45 -28



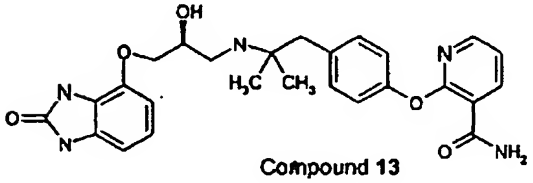
28 Compound 9 -33 -60



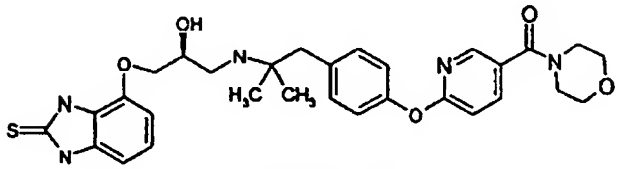
Compound 11 -8 -12.9



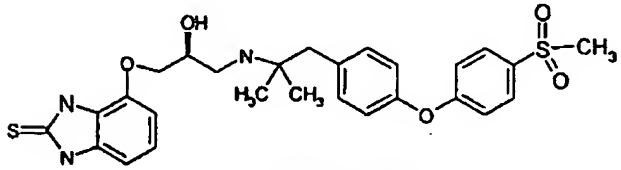
Compound 12 -17 -13



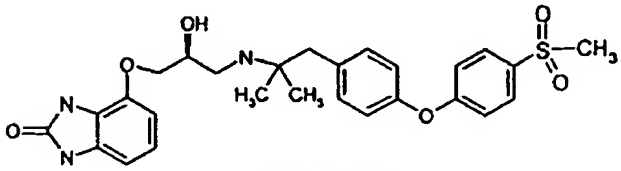
Compound 13 -22 -19



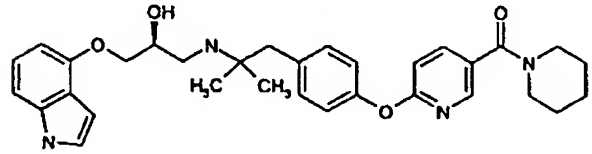
Compound 15 -18 -15



Compound 16 -1 -5



Compound 17 -10 -6



Compound 18 -33 -18

* The percent decrease in SUN in the blood of animals treated with the indicated test compound at 24 hours post treatment compared with the baseline (T = 0) SUN value for each individual. Values presented are the mean of five animals.

** The percent decrease in SUN in the blood of animals treated with the indicated test compound at 48 hours post treatment compared with the baseline (T = 0) SUN value for each individual. Values presented are the mean of five animals.

%ΔSUN is calculated as described in Example 17.

As can be seen from the results in Table 2, Compounds **1-15** and **18** are strongly anabolic at 24 and 48 hours after administration.

Example 19 - Effect of Compound **4** on Cattle

Compound **4** was found to increase muscle and decrease fat content in cattle during a twenty-eight (28) day study. Thirty-two Angus crossbred steers were blocked by weight into a heavy (4 heaviest blocks, avg. initial BW=1226 lb. (557 kg)) and a light (4 lightest blocks, avg. initial BW=1164 lb. (528 kg)) replication. The steers within each block were assigned to one of four treatments (8 steers/treatment) to investigate the effects of orally administered Compound **4** on the growth and carcass measurements when fed to cattle for 28 days immediately prior to slaughter. The treatments included a CONTROL (0.0 mg Compound **4** per kg BW), and three levels of Compound **4** (LOW, 0.125 mg Compound **4** per kg BW; MED, 0.250 mg Compound **4** per kg BW; HIGH, 0.500 mg Compound **4** per kg BW). Compound 4 was mixed with ground corn and fed to the steers as a top dress on a portion of daily feed. The CONTROL steers received a similar amount of a ground corn top dress. The steers were required to consume the initial feed and top

dress before the remaining amount of feed was issued. The basal ration was a commercially available feed (19.3% CP, DM basis). Both feed and water were available *ad libitum*. The steers were individually housed in 12 ft X 48 ft pens equipped with an individual feed bunk and automatic water supply. On day 28 the steers were weighed and a blood sample collected prior to being shipped for slaughter and subsequent carcass evaluation.

Live performance parameters were improved with the cattle on the Compound 4 treatments. LOW, MED, and HIGH exhibited a 54% to 73% increase in average daily gain (ADG, pounds/day) over CONTROL (6.31, 7.07, 6.74, and 4.08, respectively; $P<0.0002$; Figure 1). Daily dry matter intake did not differ ($P>0.47$) between the treatments. Feed efficiency (pound of feed per pound of gain) was improved ($P<0.0006$) on LOW, MED, and HIGH compared to CONTROL (4.36, 4.19, 4.18, and 7.04, respectively; Figure 2).

Carcass composition including % fat, % protein, % moisture, and % bone were calculated using the equations reported by Hankins, O.G., and Howe, P.E. 1946. U.S. Department of Agriculture Technical Bulletin No. 926 pp. 1-20. The carcass composition did not differ statistically ($P>.12$) among the treatments for any of the components, but % fat was numerically(~1.2 to ~2.7%) less with the Compound 4 treatments than the CONTROL. However, because of the heavier carcass weights observed with the LOW, MED, and HIGH treatments, the calculated yield or pounds of protein and moisture (Figure 3) were significantly greater ($P<.0036$) than CONTROL (Protein- 115.8, 115.1, 115.8, 103.1 lb (52.6, 52.3, 52.6, 46.8 kg); moisture- 389.2, 384.7, 393.4, 345.3 lb (176.7, 174.7, 178.6, 156.8), respectively).

In conclusion, feeding Compound **4** to these steers resulted in improved efficiency of gain due to a 54 to 73% greater weight gain on the same amount of feed. The extra carcass weight was due primarily to an increased amount of muscling.

Example 20 - Effect of Compounds **1** and **4** on Mice

Mice treated with Compounds **1** and **4** were found to exhibit anabolic effects. This experiment utilized ob/ob mice weighing between 65 and 82 grams. Compounds **1** and **4** were prepared in saline at a concentration of 0.15 mg/ml (.3mg/kg) or .05 mg/ml (.1mg/kg). In this way the subcutaneous injection volume was .2 ml/100 grams body weight. The dose of Compounds employed was previously shown to provide a sub-maximal blood urea nitrogen (BUN) response. It was necessary to keep the cyanopindolol warm prior to administration to keep it in solution. The treatment assigned to groups of 5 animals, each of which are shown below. Blood samples were taken via tail snip using two microhematocrit capillary tubes (heparinized) at zero and 24 hour intervals. The capillary tubes where spun down and plasma was processed for urea nitrogen levels using the Sigma 20 BUN (Rate) kit and the Monarch multi-analyzer.

Group	Treatment
1	Vehicle .2 ml/100 gram body weight + Vehicle .2 ml/100 gram body weight after 30 minutes
2	cyanopindolol .3 mg/kg body weight + vehicle .1 ml/100 gram body weight after 30 minutes
3	cyanopindolol .3 mg/kg body weight + Compound **4** .1mg/kg body weight after 30 minutes
4	cyanopindolol .3 mg/kg body weight + Compound **1** .1 mg/kg body weight after 30

minutes

5 vehicle .2 ml/100 gram body weight + Compound **1** .1mg/kg body weight after 30 minutes

6 vehicle .2 ml/100 gram body weight + Compound **4** .1mg/kg body weight after 30 minutes

7 propranalol .3 mg/kg body weight + vehicle .1ml/100 gram body weight after 30 minutes

8 propranalol .3 mg/kg body weight + Compound **4** .1mg/kg body weight after 30 minutes

9 propranalol .3 mg/kg body weight + Compound **1** .1mg/kg body weight after 30 minutes

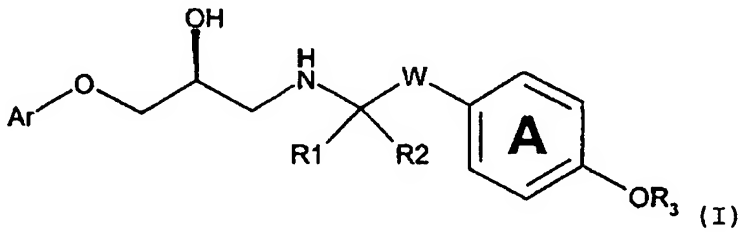
The beta blockers cyanopindolol and propranolol do not appear to reverse the BUN lowering effects of Compounds **1** and **4** in ob/ob Mice. This result is consistent with these compounds exerting anabolic effects by acting at a receptor other than beta 1, beta 2 or beta 3.

Those skilled in the art will be able to recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS

What is claimed is:

1. A method of treating a subject with a wasting syndrome, said method comprising the step of administering to the subject an effective amount of a compound represented by Structural Formula I:



(I)

and physiologically acceptable salts thereof, wherein:

Ar is a substituted or unsubstituted aryl group;

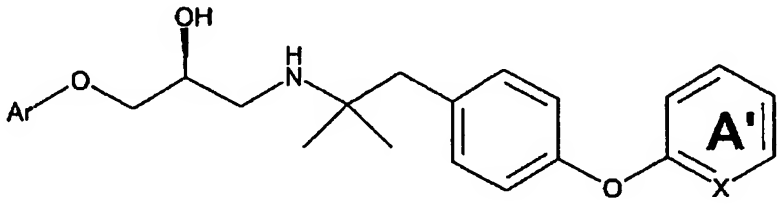
Ring **A** has zero, one or two additional substituents;

R1 and R2 are independently -H or a C1-C4 alkyl group;

W is $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$; and

R3 is a substituted with one, two or three substituents or unsubstituted phenyl or pyridyl group.

2. The method of Claim 1 wherein the compound is represented by Structural Formula II:



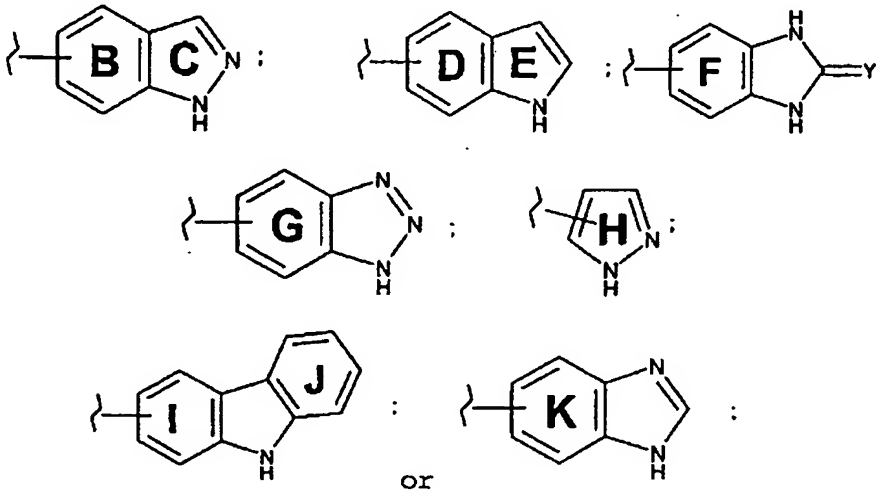
(II)

wherein:

Ring A' is unsubstituted or substituted with one or two substituents; and X is -N- or -CH-.

3. The method of Claim 2 wherein the wasting syndrome is a loss of muscle mass resulting from AIDS, cancer, cancer therapy, aging, muscle denervation, dystrophic disease, an eating disorder, or muscle deconditioning.

4. The method of Claim 3 wherein Ar is represented by a structural formula selected from:



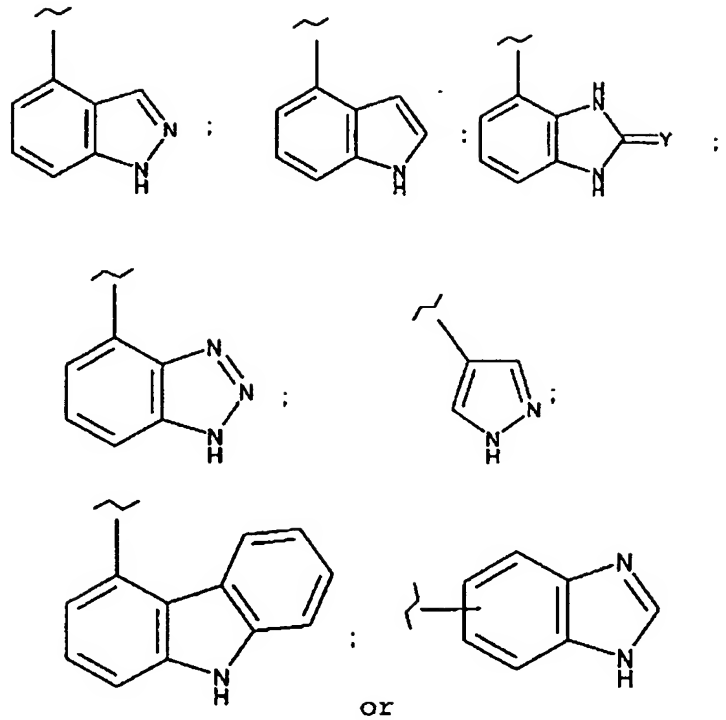
or

wherein:

Rings B-K are independently substituted with one or two substituents or unsubstituted; and

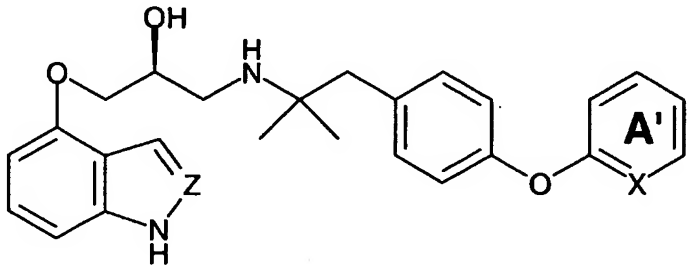
Y is S or O.

5. The method of Claim 4 wherein Ar is represented by a structural formula selected from:



or

6. A method of treating a subject with a wasting syndrome, said method comprising the step of administering to the subject an effective amount of a compound represented by Structural Formula III:



(III)

and physiologically acceptable salts thereof, wherein Ring **A'** is substituted with one or two substituents or unsubstituted; -X- is -CH- or -N-; and Z is -N- or -CH-.

7. The method of Claim 6 wherein:

Ring **A'** is monosubstituted with R4;

R4 is selected from -CONR5R6, -SO_nR7, -CN, -OH, halogen, C1-C4 haloalkyl, -COOR8, -COOH or tetrazolyl;

R5 and R6 are independently -H, C1-C4 alkyl, or, taken together with the nitrogen atom to which they are bonded, form a five to seven membered non-aromatic heterocyclic group;

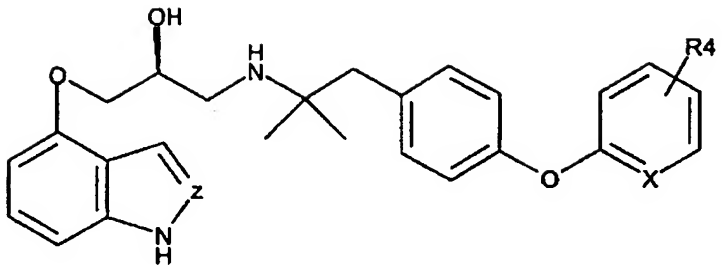
R7 and R8 are independently -H or C1-C20alkyl;and

n is 0, 1, or 2.

8. The method of Claim 7 wherein the wasting syndrome is a loss of muscle mass resulting from AIDS, cancer, cancer therapy, aging, muscle denervation, dystrophic disease, an eating disorder, or muscle deconditioning.

9. The method of Claim 8 wherein R5 and R6 are independently -H, C1-C4 alkyl, or, taken together with the nitrogen atom to which they are bonded, form a morpholinyl or piperidinyl group.

10. A method of treating a subject with a wasting syndrome, said method comprising the step of administering to the subject an effective amount of a compound represented by Structural Formula IV:



(IV)

and physiologically acceptable salts thereof,

wherein:

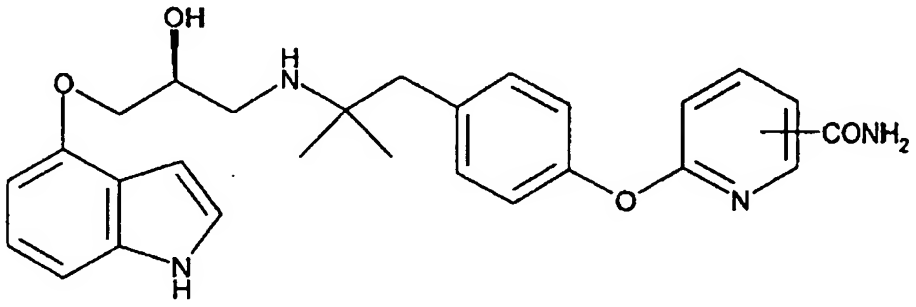
X is -CH- or -N-;

Z is -N- or -CH-; and

R4 is -CN, $-CONH_2$ or $-SO_2CH_3$.

11. The method of Claim 10 wherein the wasting syndrome is a loss of muscle mass resulting from AIDS, cancer, cancer therapy, aging, muscle denervation, dystrophic disease, an eating disorder, or muscle deconditioning.

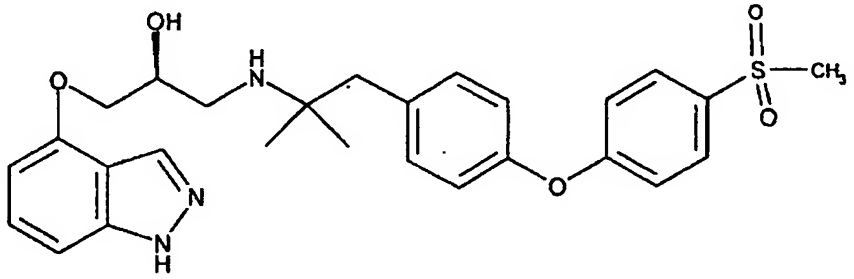
12. A method of treating a subject with a wasting syndrome, said method comprising the step of administering to the subject an effective amount of a compound represented by the following structural formula:



and physiologically acceptable salts thereof.

13. The method of Claim 12 wherein the wasting syndrome is a loss of muscle mass resulting from AIDS, cancer, cancer therapy, aging, muscle denervation, dystrophic disease, an eating disorder, or muscle deconditioning.

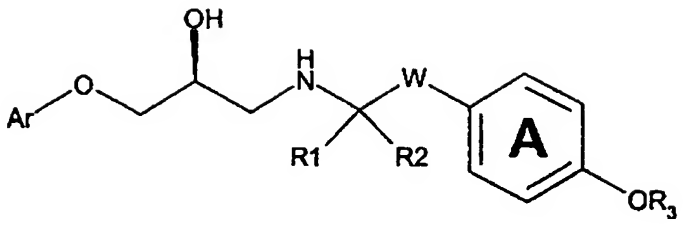
14. A method of treating a subject with a wasting syndrome, said method comprising the step of administering an effective amount of a compound represented by the following structural formula:



and physiologically acceptable salts thereof.

15. The method of Claim 14 wherein the wasting syndrome is a loss of muscle mass resulting from AIDS, cancer, cancer therapy, aging, muscle denervation, dystrophic disease, an eating disorder, or muscle deconditioning.

16. A method of promoting muscle growth in a human subject, comprising administering to the subject an effective amount of a compound represented by the following structural formula:



wherein:

Ar is a substituted or unsubstituted aryl group ring;

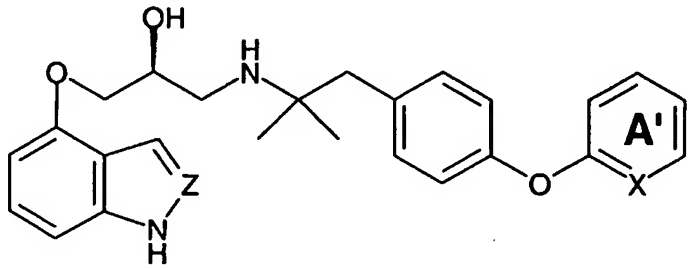
Ring **A** has zero, one or two additional substituents;

R1 and R2 are independently -H or a C1-C4 alkyl group;

W is $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$; and

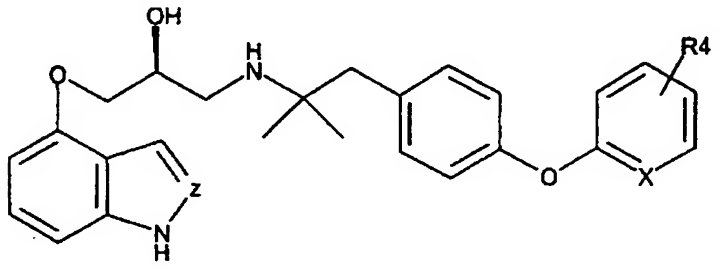
R3 is a substituted with one, two or three substituents or unsubstituted phenyl or pyridyl group.

17. A method of promoting muscle growth in a human subject, comprising administering to the subject an effective amount of a compound represented by the following structural formula:



and physiologically acceptable salts thereof, wherein Ring **A'** is substituted with one or two substituents or unsubstituted; X is -CH- or -N-; and Z is -N- or -CH-.

18. A method of promoting muscle growth in a human subject, comprising administering to the subject an effective amount of a compound represented by the following structural formula:



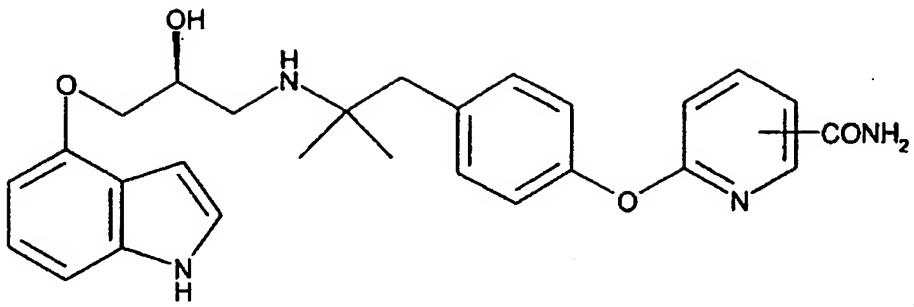
and physiologically acceptable salts thereof, wherein:

X is -CH- or -N-;

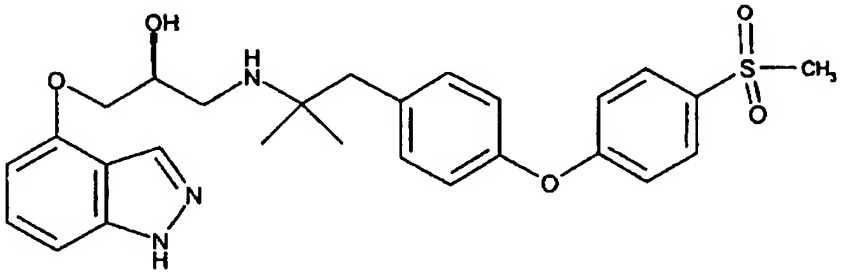
Z is -N- or -CH-; and

R4 is -CN, $-CONH_2$ or $-SO_2CH_3$.

19. A method of promoting muscle growth in a human subject, comprising administering to the subject an effective amount of a compound represented by a structural formula selected from:



or



and physiologically acceptable salts thereof.

20. A compound of Structural Formula (I), or a pharmaceutically acceptable salt thereof, for use in treating a wasting syndrome.

21. A compound of Structural Formula (I), or a pharmaceutically acceptable salt thereof, for use in promoting muscle growth in a human subject.

22. Use of a compound of Structural Formula (I), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a wasting syndrome.

23. Use of a compound of Structural Formula (I), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for promoting muscle growth in a human subject.

24. A compound as described in any one of the foregoing claims 1-19, or a pharmaceutically acceptable salt thereof, for use in treating a wasting syndrome.

25. A compound as described in any one of the foregoing claims 1-19, or a pharmaceutically acceptable salt thereof, for use in promoting muscle growth in a human subject.

FIG. 1

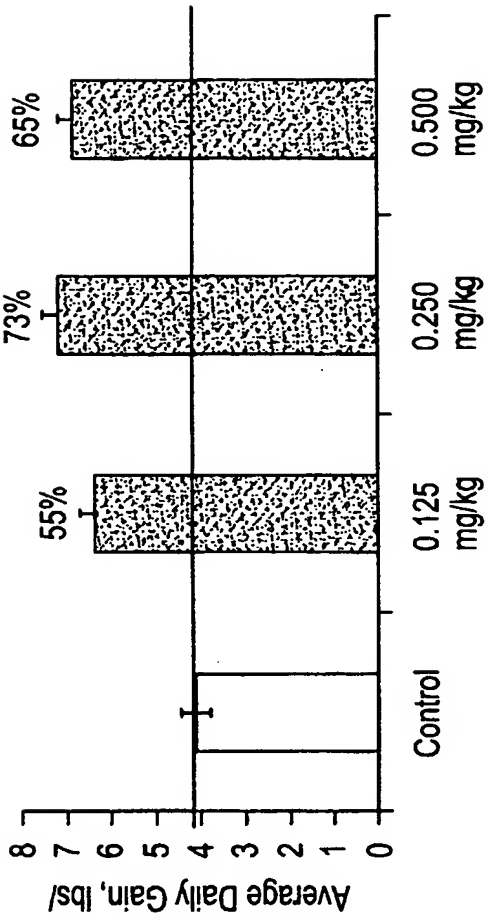

Average Daily Gain, lbs/
0
1
2
3
4
5
6
7
8
Control
0.125 mg/kg
0.250 mg/kg
0.500 mg/kg
55%
73%
65%

FIG. 2

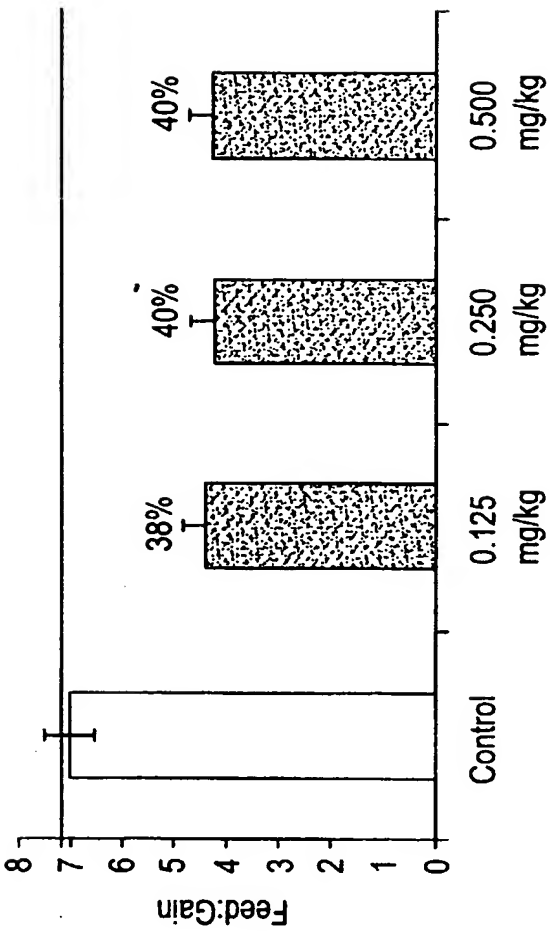
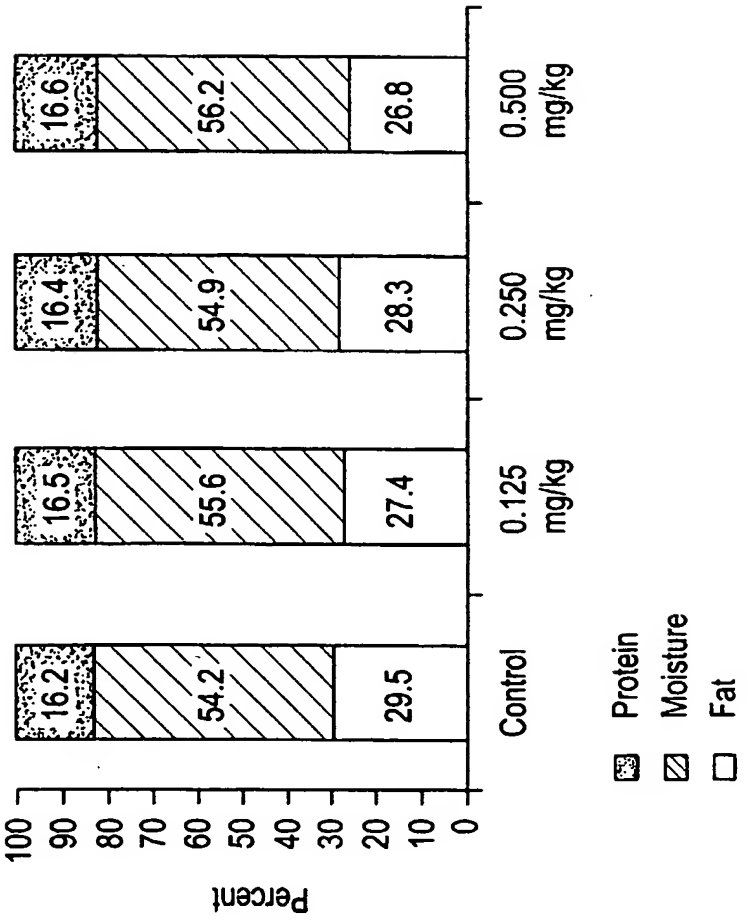

Feed:Gain
0
1
2
3
4
5
6
7
8
Control
38%
0.125 mg/kg
40%
0.250 mg/kg
40%
0.500 mg/kg

FIG. 3


Percent
100
90
80
70
60
50
40
30
20
10
0
16.2
54.2
29.5
16.5
55.6
27.4
16.4
54.9
28.3
16.6
56.2
26.8
Control
0.125 mg/kg
0.250 mg/kg
0.500 mg/kg
Protein
Moisture
Fat